PATENT SPECIFICATION (11) 1 561 100

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(21) Application No. 52098/76 (22) Filed 14 Dec. 1976 (19)

(31) Convention Application No's 640608 (32) Filed 15 Dec. 1975 in
640651
640612
640610
640609
641068
640655
640654
640653
640652

(33) United States of America (US)

(44) Complete Specification Published 13 Feb. 1980

(51) INT. CL.[3] A61K 9/70

(52) Index at Acceptance
A5B 832 833 835 836 839 M N

(54) NOVEL DOSAGE FORM

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124 - 184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

Abstract of the Disclosure

Pharmaceutical unit dosage forms comprise an edible web having deposited thereon or at least partially thereon at least one medicament, the web being thereafter fabricated and finished to pharmaceutical solid unit dosage forms having no medicament exposed on an exterior surface. The dosage forms have a consistency of release of medicament which can be controlled to exacting specifications. The disclosed solid unit dosage forms can be prepared by high speed automated equipment, and a preferred method by which they are made is characterized by non-destructive quality control analysis and performance evaluation both conducted on-line and integrated into the manufacturing operation. Included in the scope of the disclosed invention are certain systems and methods of manufacture.

Background of the Invention

The orally administered solid unit dosage forms heretofore recognized in the pharmaceutical industry are generally divisible into two basic forms, i.e. tablets and capsules. There are various broad categories of both tablets and capsules recognized in the art such as, for example, those which are enteric coated to release medication in the intestinal tract, those which, by various mechanisms, release medication over an extended period of time, effervescents and the like. By and large such conventional solid oral dosage forms suffer from a number of disadvantages.

First, conventional solid oral unit dosage forms are disadvantageous in that each contains, admixed with the active ingredient, a plurality of various substances which are termed "therapeutically inert or non-toxic, pharmaceutical adjunct materials". Such materials fall under the art-recognized categories of diluents, excipients, binders, lubricants, disintegrants, stabilizers, buffers, preservatives and the like. Although these materials are recognized as indispensible in the art of pharmaceutical compounding, their use nonetheless presents problems which must be dealt with from a viewpoint of cost, final size and weight of the dosage unit and the like. Additionally, each such adjunct material must be evaluated before use in terms of potential incompatabilities with the medicaments present. Further, certain of these materials, e.g. lubricants, may present problems concerning the bioavailability of the active ingredient. Also, the presence of such materials must be considered in analytical procedures utilized to test for potency etc. of the finished dosage form.

A second primary disadvantage in solid oral unit dosage forms known to the art is that the methods available for assay thereof involve destruction of the dosage form thereby permitting the testing of only a small percentage of such forms actually produced.

Therefore, it is recognized in the art that there can be considerable deviation within a given batch of such dosage forms since the mean of dosage, performance, etc. for each batch deviation is determined by analysis of a relatively minor number of samples.

The batch concept in itself is a disadvantage to prior art oral solid dosage forms simply in view the economics of the batch designation, control and evaluation.

The present invention is intended to provide solid dosage units, primarily for oral ingestion which are producible in large numbers at high speed and which they are prepared by a method unique in the pharmaceutical industry, do not suffer from the above enumerated disadvantages of currently available solid oral dosage forms, i.e. tablets and capsules. This method is highly advantageous in that it: eliminates the necessity for batch requirements as they are conventionally recognized; provides for continuous on-line analysis for potency as well as on-line performance evaluation of the dosage forms as they are being produced; permits the substantial elimination of the necessity of mixing conventional pharmaceutical adjunct materials with the medicaments, with the exception of glidants which may be required to facilitate the flow of powders and/or certain other materials advantageous for product performance; and provides pharmaceutically elegant unit dosage forms which can be engineered to release medicament at any desired rate and which are capable of a rate of release faster than commercial tablets and capsules presently available. In summary, the dosage forms of the invention provide assurance that a larger percentage of a more accurately measured amount of medication will be available in a more precisely controlled time after ingestion than is the case with present commercial units.

The oral unit dosage forms of the present invention are advantageous in a number of important respects, foremost of which is the fact that they are substantially qualified by on-line procedures during high-speed, substantially automated manufacturing operations. In addition, the dosage forms of the present invention are also advantageous in that the medicament contained therein is released for absorption with exceptional uniformity over a large number of dosage units. Further, the dosage units of the invention can be engineered to release medication within a shorter period of time after ingestion than is possible with solid oral dosage forms, e.g., tablets and capsules, presently available. Therefore, the dosage units of the invention provide consistency both in content of medicament and release thereof for absorption.

Regarding the prior art, the following publications, which are directed to solid dosage forms distinguishable from conventional tablets, are noteworthy. Russell, U.S. Patent 3,444,858 issued May 20, 1969, describes a vehicle for the buccal administration of medicaments comprising a strip of gelatinous material containing medication, said strip being divided into sections each of which is connected to the next by easily tearable ligaments. In use, a section is merely separated from the strip and placed in the mouth.

A second publication warranting mention is an article in the New England Journal of Medicine, Vol. 289, No. 10,pp. 533-5 (1973). This article describes a means whereby birth control medication is being made available to women in the People's Republic of China on a very large scale. In this method, a sheet of colored, water-soluble, carboxymethylcellulose paper is treated with a solution of progestational and estrogenic materials. The sheet is then perforated and cut into strips. The medicament is packaged as a strip of 22 "squares" which are torn from the strip and taken daily. This method does not provide for the concealment of the drug in the final dosage form, thereby suffering from the disadvantage of potential contamination and/or inactivation of the medication once the package is opened. Further, in consequence of not being completely unitized, such perforated strips can give rise to uneven tearing at the perforations and potentially dispropotionate dosage.

Finally to be considered is Higuchi et al. U.S. Patent 3,625,214 issued December 7, 1971, which describes a dosage form utilized for controlled, i.e. sustained, release of medicaments. The dosage form is comprised, in essence, of a medicament containing matrix which is coated on a substrate which is then spiral wound to a final "jelly roll" appearance. After ingestion, the medicament is released by the gradual erosion of the outer layers of substrate and also by diffusion from the sides where there is exposed medicament. There is no disclosure of whether the disclosed dosage forms are amenable to high capacity pharmaceutical manufacturing. There is further no disclosure of means whereby the disclosed dosage forms can be turned into pharmaceutically elegant finished products.

In distinct contrast to the teachings of the foregoing publications, the present invention is intended to provide novel solid dosage units which are completely unitized, are amendable to non-destructive, on-line analytical testing during high capacity pharmaceutical manufacturing operations, are essentially free from pharmaceutical adjunct materials that may interfere with performance, have no exposed medicament and have a superior consistency of release of medicament which enhances the efficacy thereof.

Brief Statement of the Invention

The present invention provides solid pharmaceutical unit dosage forms, primarily for oral administration, comprising a plurality of layers of an edible therapeutically inert web, at least one of said layers having a composition comprising one or more medicaments bonded to one or more surfaces, said layers of web being arranged so as to have substantially no medicament loaded to an outer surface thereof, said layered arrangement of web being sealed so as to completely internalize the medicament. The unit dosage forms can be prepared by high capacity pharmaceutical manufacturing techniques utilizing, in certain instances, novel apparatus. The manufacturing process preferably includes means to non-destructively test the dosage forms on-line to determine the amount of medicament which has been loaded to the web prior to the fabrication thereby assaying the potency of the finished dosage units by physical parameters.

Detailed Description of the Invention

The present invention is directed to solid, unit dosage forms primarily for oral ingestion which are advantageous in a number of particulars over present solid oral dosage forms, i.e. tablets and capsules. First, the fact that the dosage units of the invention are substantially free of conventional pharmaceutical adjunct materials results in a saving in cost of raw materials and manufacturing procedures as well as eliminating potential incompatibilities caused by the presence of such materials. The distinction must be made here between the webs of the invention which can be considered adjunct material and the materials such as fillers, binders and the like which are admixed with the medicament in prior-art solid dosage forms.

Second, insofar as the solid unit dosage forms of the invention are prepared continuously and subjected to on-line, non-destructive analytical procedures, the requirement for batch lot manufacturing as it is known today is eliminated thereby realizing a considerable economic saving and a substantially improved level of quality control viewed in terms of the finished dosage units. Provided, that the manufacturing operation of the invention includes means to feed back information from a testing station to the manufacturing procedures immediately preceding it, on-line corrections and adjustments can be effected. Such means facilitate the removal of only a small number of dosage units from any number designated as a manufacturing lot, i.e. from the positive reading immediately preceding a negative reading to the next following positive reading. The designation and removal of such small quantities of dosage forms thus avoids "poisoning of the barrel" and realizes both a large economic advantage over present pharmaceutical manufacturing procedures and a superior level of quality control particularly in terms of the active ingredient content in the finished dosage forms. In normal operation, the dosage forms of the invention are manufactured by time lot procedures, i.e. a "lot" of dosage forms constitutes the number prepared between two given points in time. This concept is believed to be unique in the pharmaceutical industry. It will be appreciated, however, that some destructive testing will be required in any pharmaceutical manufacturing procedure as a check of performance of the finished product. Such testing is, however, required to a materially smaller degree in the preferred procedures of the subject invention than in prior-art manufacturing operations. More important, however, is the fact that such destructive procedures, i.e. performance evaluation procedures, are carried out on-line, with the information feed back thus realizing the benefits discussed above regarding the nondestructive procedures.

Third, the solid oral dosage units of the present invention are unique in that they differ from prior-art tablets and capsules in appearance, shape, texture, etc. and therefore have the advantage of being easily identified. Also, the preferred on-line non-destructive testing procedures and continuous manufacturing operations of the present invention facilitate packaging of the unit dosage forms of the present invention on-line into individual containers such as, for example, clear plastic strips of blister packages, thereby saving costs in handling and equipment.

Fourth, the exactness of the preparation of solid dosage forms of the present invention, i.e. the uniformity of deposition of the medicament on the web and the precision in shaping of the final units, combined with the desirable characteristics of the web itself, enable the finished dosage forms to easily meet stringent specifications of size, shape, release of medicament and the like. The dosage forms of the invention also possess excellent stability and are amenable to the incorporation of medicaments which are recognized as being adversely affected by moisture since, in certain embodiments of the present invention, the medicament is deposited or loaded to the web by electrostatic deposition, thereby providing an almost total absence of moisture which might cause an adverse reaction to take place. Also, where the dosage forms of the present invention are fabricated from a laminate of sheets of web, medicaments recognized in the art of pharmaceutical compounding as being chemically incompatible can be deposited upon alternate sheets of web. This effectively

stabilizes such combination without the need to resort to such economically unattractive measures as the coating of one or more of such incompatible substances with an insulating material, the admixture of stabilizing adjunct materials with such medicaments, the incorporation of such medicaments into separate tablet layers which are then pressed together and the like. The adoption of either or both of these procedures, i.e. the deposition of a medicament on the web electrostatically as a dry powder, and the placing of potentially incompatible medicaments alternately between sheets of a laminate, enables the dosage forms of the invention to be advantageously useful in the administration of effervescent formulations.

The solid oral dosage forms of the present invention are further unique in that the medicament contained therein is completely internalized within the dosage form yet, in most instances, there is no coating per se applied to the finished dosage form. This represents an additional economic advantage for the dosage forms of the subject invention over prior-art tablets, which must be coated to obtain internalization of the medicament.

While the dosage forms prepared in accordance with the methods of the present invention are intended primarily for oral administration, dosage forms suitable for rectal and/or vaginal administration are likewise contemplated. Modifications in the size of the web as well as the fabrication methods to be described hereinafter to produce dosage forms of the desired size and shape will be readily apparent to those skilled in the art. Certain modifications of the web composition to obtain the desired type and pattern of release of medicament would likewise have to be made. Tests have shown that rectal and vaginal insertion of solid dosage forms according to the invention has produced substantially no local irritation.

As mentioned above, the novel dosage units prepared in accordance with the invention can be formulates or "engineered" to any desired release pattern including sustained release. Regardless of the release pattern, the dosage units of the invention are characterized by an exceptional uniformity of release over a large number of dosage units, e.g. ten thousand or more. The variance in release rate can be obtained in accordance with the present invention by the manipulation of a number of factors such as, for example, the thickness of the web, the composition of the web, the presence of an overwrap or outside seal on the fabricated web and its composition, how tightly the web is fabricated, and the like. For example, a web composition containing a high content of sodium carboxymethylcellulose will normally disintegrate slowly in gastric fluids. Dosage forms fabricated from such webs by fan-folding as will be described hereinafter will open or unfold upon contact with gastric fluid, thereby releasing the medicament loaded on the internal surfaces thereof very rapidly, in fact, more rapidly than conventional tablets and capsules presently available. However, if such a fan-folded dosage form were to be sealed on the folded edges with a substance such as, for example, ethylcellulose, cellulose acetate phthalate or zein, which will prevent its opening in gastric fluids, the medicament would become available by the gradual erosion of the web thereby giving a steady, sustained release of medication. Since the dosage forms prepared in accordance with the present invention are capable of releasing medication with a rapidity superior to presently available solid dosage forms, i.e. tablets and capsules, such release represents the preferred embodiment of the present invention.

The accompanying drawings are summarized as follows:

Figure 1 is a block diagram of a total manufacturing process, indicating points of on-line inspection,

Figure 2 is a diagrammatic representation of a system capable of effecting the process depicted in Figure 1,

Figure 3 is a diagrammatic representation of an arrangement for carrying out the convolute winding technique of dosage form fabrication,

Figure 4, *4A* and *Figure 5* illustrate rotary-forming and lamination techniques of dosage form fabrication,

Figures 6A-6D illustrate the finishing and sealing aspects of the fan-folding technique of dosage form fabrication, and

Figures 7 and *8* are graphs showing the pattern of release of active ingredient from the dosage forms of the invention in comparison with a prior-art solid dosage form, i.e. a capsule.

The Web

The webs capable of being utilized for deposition for medicament in accordance with the present invention must meet a large, diverse number of physical and chemical criteria to be completely acceptable in the practice of the invention. These criteria can be briefly summarized as follows:

The web must be non-toxic and edible, and, particularly, must not have an objectionable

"feel" in the mouth. In addition, the web preferably self destructs or is degradable in body fluids and/or enzymes. However, the web can be of non-destructible substances which is readily eliminated by the body. The web preferably is hydrophilic and readily disintegrable in water. These properties must not be adversely affected and, preferably, will be enhanced at the pH of gastric fluid;

The web must be totally inert to the medicament loaded thereto and must not release any substance upon dissolution with gastric fluid which would cause an *in situ* incompatibility with said medicaments;

The web must be stable over extended periods of time and at elevated temperatures and relative humidity and generally be a poor medium for the growth of microorganisms;

The web must have acceptable resistivity properties so that powdered medicament (usually possessing dielectric properties) can be loaded thereto by electrostatic deposition;

The web must possess acceptable workability and mechanical properties, i.e. it must possess sufficient elasticity to allow it to be drawn or cast into a thin sheet, i.e. from about 0.025mm to about 0.25mm in thickness; it must possess good tensile strength and tear strength; and it must have acceptable fold endurance where required to withstand certain of the fabrication methods as will be described hereinafter;

The web surface must facilitate the adoption of those types of on-line analytical procedures which are described hereinafter, be capable to being coated with and retain powdered medicament electrostatically or otherwise loaded thereto and be amenable to printing operations;

The web must be readily sealable by liquid and/or heat-seal methods such as are recognized in the art. The sealing, however, must be effective at levels of moisture and heat which do not adversely affect the medicament contained in the dosage form. In addition, the web must possess acceptable flammability resistance so as to tolerate such sealing operations;

In certain instances the web must possess "memory", i.e. it must have sufficient resiliency so that, upon contact with gastric fluids, it will very rapidly reverse the fabrication process and "open" thus releasing medication for absorption. By "opening" is meant that, for example, if the dosage form is fabricated by fan-folding it will open like a bellows, and if fabrication is by convolute winding it will uncoil.

The web must possess other properties such as, for example, having acceptable taste and odor, which will become apparent to those skilled in the art from the instant disclosure.

As mentioned above, the webs utilized in the present invention are preferably water soluble or water dispersible. There are two basic mechanisms whereby the webs of the present invention are formulated to self destruct in contact with water or gastric fluid. First, the web can contain particles of substance such as, for example, casein, gelatin and the like which swell upon contact with water thereby disrupting or breaking the web. Second, the web formulation may contain both water soluble and insoluble constituents. Upon contact with water, the soluble constituents of such a formulation will tend to go into solution and the insoluble constituents to precipitate thereby causing the web to rupture. The latter means of disrupting the web is not as rapid as the former. Examples of suitable water soluble constituents include methylcellulose and the like. Examples of suitable water insoluble constituents include ethylcellulose, and the like.

The web formulations utilized in preparing the novel dosage forms of the present invention are of two basic types, i.e. polymeric and paper. The polymeric formulations generally comprise;

a) one of more organic film formers
b) one or more plasticizers
c) modifiers, i.e. other ingredients optional with certain formulations such as disintegrants, extenders and the like.
d) one or more fugitive solvents.

The paper formulations generally comprise:

a) one or more fibrous materials
b) one or more non-fibrous modifiers, i.e. other ingredients optional with certain formulations, e.g. one or more organic film formers, disintegrants, extenders and the like.
c) a fugitive solvent.

The film forming constituent of the polymeric webs which may be used for the purposes of the present invention comprises one or a mixture of art-recognized, non-toxic, organic film formers such as, for example, natural and chemically modified starches and dextrins, proteins such as gelatin; cellulose derivatives such as sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose and the like; other polysaccharides such as pectin, acacia, xanthin gum, guar gum, algin and the like; synthetics such as polyvinylpyrrolidone, polyvinyl alcohol and the like. Preferred film formers are hydroxypropylcellulose and sodium carboxymethylcellulose. Although the concentration of the film

forming component in the polymeric web is not particularly critical to the practice of the invention, it has been found that between about 5% by weight and about 95% by weight is to be preferred, with a concentration of from about 40% by weight to about 90% by weight being most preferred.

The above named film forming substances are equally illustrative of the film forming component of the paper web formulations which may be used for the purposes of the present invention where such is present. Preferred film formers of these paper web formulations are likewise hydroxypropylcellulose and sodium carboxymethylcellulose. The concentration of the film forming ingredient in the paper web formulations is likewise not considered critical. However, when such ingredient is present to act as a binder or disintegrant for the fibrous material, it should usually not exceed about 40% by weight, preferably from about 2% by weight to about 20% by weight and most preferably from about 4% by weight to about 10% by weight.

The fibrous ingredient of the paper web formulations which may be used for the purposes of the invention can be any of the commercially available natural or artifical fibers which have been shown by proper tests to be non-toxic. Examples of such fibers include cotton, linen, cellulose, synthetically modified cellulose, rayon, textured vegetable protein, collagen and the like.

To insure the required workability and mechanical properties, the polymer webs utilized in the practice of the invention contain an effective amount of a plasticizing ingredient. Such ingredient may include one or more members of the group of plasticizers recognized in the art of pharmaceutical compounding such as, for example, glycerin, the polysorbates, e.g. polysorbate 80, polysorbate 60, certain mixtures of mixed mono- and di-glycerides of saturated fatty acids and the like. It is preferred that such plasticizers be present in an amount comprising from about 1% by weight to about 60% by weight, preferably from about 10% by weight to about 50% by weight of the web composition.

Both polymer and paper webs may contain one or more disintegrants such as are recognized as being conventional in the art of disposable paper such as, for example, various types of starches, casein, gelatin and the like. The webs for use according to the invention should contain from about 0% by weight to about 40% by weight preferably from about 5% by weight to about 20% by weight of disintegrant depending on the web formulation.

Further, both types of web formulations may contain one or more fillers or extenders which are recognized in the art as being conventional. Such ingredients include, for example, opacifier fillers such as titanium dioxide, chalk, kaolin and the like, microcystalline cellulose, calcium carbonate and the like. It is to be appreciated that some of the ingredients enumerated herein can function in more than one capacity and therefore fall under more than one of the categories listed above. For example, calcium carbonate can function as both an opacifier and dispersant, certain starches can function as binders and as disintegrants, etc.

In addition, both polymer and paper formulations may contain one or more modifying ingredients which affect the electrical, mechanical, optical or permeative properties of the webs produced therefrom. Examples of such ingredients include an electrolyte such as, for example sodium chloride, potassium chloride and the like, surface active agents such as dioctyl sodium sulfosuccinate and the like. The webs may also contain optical ingredients such as pharmaceutically acceptable coloring agents, preservatives, and the like.

Finally, both types of web formulations, in most instances, will contain a fugitive solvent, e.g. water, certain organic solvents, for example, ethyl alcohol or combinations of such solvents i.e. a hydroalcoholic mixture which is removed during formulation of the web.

Specific examples of film compositions for use in accordance with the present invention include the following:

Polymeric films that self-destruct in an aqueous environment due to the presence of swelling agents.

	Ingredient	*Percent by Weight*
I	Hydroxypropylmethyl-cellulose	45.69
	Acacia	19.44
	Gelatin, extra fine, solubilized	32.08
	Dioctyl Sodium Sulfosuccinate 75% aqueous solution	0.09
	Titanium dioxide	1.94
	Lecithin	0.75
		100
II	Refined starch	33.06
	Carboxymethylcellulose	33.06
	Propylene Glycol	33.06
	Sodium Benzoate	0.55
	Sorbic Acid	0.28
		100
III	Hydroxypropylmethylcellulose	55.19
	Cellulose Acetate Phthalate	2.99
	Corn Starch	28.66
	Propylene Glycol	9.87
	Titanium Dioxide	1.52
	Dioctyl Sodium Sulfosuccinate	1.52
	Lecithin	0.25
		100
IV	Hydroxypropylmethyl-cellulose	64.00
	Cellulose Acetate Phthalate	3.10
	Calcium Carbonate	21.74
	Propylene Glycol	9.06
	Titanium Dioxide	0.91
	Dioctyl Sodium Sulfosuccinate	0.91
	Lecithin	0.30
		100

All of formulations I-IV are sealable by the application of heat and pressure. Formulation IV self-destructs in an aqueous environment due to the presence of insoluble polymeric agents.

Preferred paper formulations for use in accordance with the subject invention comprise from about 70% by weight to about 99% by weight, more preferably from about 90% by weight to about 96% by weight fiber, e.g. hardwood or softwood fibers or mixtures thereof, from about 1% by weight to about 30% by weight, more preferably from about 4% by weight to about 10% by weight of a disintegrant selected from sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and guar gum and from about 0% by weight to about 5% by weight, more preferably from about 0% by weight to about 2% by weight of a surfactant such as, for example, polysorbate 80, dioctyl sodium sulfosuccinate, sodium lauryl sulfate and the like; the ability of the above substances to function as disintegrants in paper formulations is considered to be unexpected in view of the fact that, where members of this groups are utilized in paper making they are present in different quantities and perform a different function. For example, wherein sodium carboxymethylcellulose has heretofore been utilized in paper making, it has been utilized in small quantities, i.e. 0.1% by weight or less, as an aid in dispersing the fibers as the paper is formed. In distinct contrast, it has been found that when sodium carboxymethylcellulose or the other substances enumerated above are added in large quantity, i.e. up to 30% by weight, after the paper web is formed, but while it is still wet, they will function as disintegrants; the time of addition of these substances is critical to the function thereof as disintegrants. The disintegrants are added as a solution preferably in the solvent utilized to prepare the paper web. It has been found that the above named disintegrants, when added to the web as herein described, coat the fibers. When the finished dosage form is contacted with water, the disintegrant swells, thus forcing the fibers to disrupt the web. The surfactants, where present, act to enhance the penetration of water to the disintegrant, thus promoting disruption.

The webs utilized in accordance with the invention are formed by processes conventional in the arts, e.g. the paper-making industries. For example, the polymeric webs can be cast on an appropriate substrate, e.g; Mylar, stainless steel, release paper and the like. (The word "Myler" is a registered Trade Mark). The webs are then dried, e.g. in a forced-air oven. The temperature of the drying air and length of drying time depend on the nature of the solvent utilized as is recognized in the art. Most of the webs contemplated herein, however, are dried at a temperature between about 25° and 105°, preferably between about 60° and 90°C.

A second method of forming polymeric webs which is conventional in the art is extrusion. This method is preferred with webs wherein the film forming ingredient is a modified food starch, hydroxypropylcellulose or other extrudable polymer. The mechanical particulars of the extrusion process, e.g. the particular equipment utilized, the extruding force, and the shape and temperature of the extrusion orifice, are considered to be within the skill of those familiar with the art, and can be varied in a known manner to achieve the physical characteristics of the webs to be described hereinafter.

The paper webs which may be used for the purposes of the subject invention are prepared utilizing conventional paper-making machinery such as, for example, Fourdrinier paper making machines. In all cases, however, the web must be uniform in both thickness and width. The webs are usually between about 1 and about 10 mils (about 0.03 mm to about 0.3 mm,) and preferably from about 1.5 to about 4.5 mils (about 0.038 mm to about 0.123 mm) thick. A convenient width for such webs is 12 inches (30cm) although the width of the web is not particularly critical to the practice of the invention. The web can be produced in any length. However, in view of the fact that the novel dosage forms produced in accordance with the invention are eminently suited to high speed manufacture, the webs should be prepared in large quantity, e.g. 15000 feet or more which can be stored, e.g. on cores or spools.

Reference is made to Figure 1 in which is shown in block diagram form the overall system process for manufacturing in large numbers the various kinds of dosage forms herein described. Block 10 of Figure 1 represents web production from formulations such as have been discussed above. As the web is produced, or shortly thereafter, it undergoes an inspection step (block 11 in Figure 1) where various examinations, which may be in whole or in part automated, are performed, to ensure the integrity of the web, as will be more particularly described hereinafter. It is to be noted, however, that the inspections of the web can take place as the web is formed or at any convenient point thereafter, either by means associated with the apparatus making the web or by other apparatus, and may, in fact be performed at another location.

The active ingredient to be deposited on the web is prepared and stored for use in container means, as is generally illustrated at 22 in Figure 2, which figure illustrates, largely

in schematic form, various pieces of apparatus suitable for performing the steps indicated in Figure 1. The prepared active ingredient whose production is represented by block 12 in Figure 1 is caused to be forwarded to an arrangement generally indicated at 23 in Figure 2 where the active ingredient particle size reduction and control represented by block 13 in Figure 1 is performed. Although this step will be discussed in greater detail hereinafter, it is intended via this step represented by block 13 and the depicted apparatus 23 to provide a uniformity of flow in order to enable exact and uniform deposition (block 14 of Figure 1) or the active ingredient on the web, which is illustrated at 24 in Figure 2. It should be noted that the system example depicted in Figure 2 pertains to the deposition of dry particulate material onto the web in a dry state. It is to be clearly understood, however, that the scope of this invention includes as well wet deposition of active ingredient onto the web. Figure 2 also illustrates schematically at 21 (in respect of the case wherein the web is prepared and stored for later use) the web inspection step (block 11 of Figure 1), which is performed, e.g., as the web is caused to be taken off of a storage roll 20. It is clearly understood that inspection may be made prior to the web wound and stored as well as or in addition to being performed where and as indicated in Figure 2 and 21. The particulars of web inspection are described in greater detail hereinafter.

With more particular regard to inspection means 21, inspection of the uncoated web can be accomplished by several methods. Holes, blemishes, and physical integrity of the web may be evaluated and quantified by using a scanning laser beam and photodetector combination. The system can be used in both transmission and reflection modes. A continuous helium-neon laser beam can be steered across the web by a mirror on a galvanometer, the mirror position being electronically controlled so that the position of any defect on the web can be located. The reflected or transmitted light can be detected by a linear photodiode located behind an interference filter to exclude room (stray) light, and the electrical output used to count the number of defects and determine their size and distribution along the length of the web, by analyzing the detector output signal with a pulse height-width analyzer.

An alternative method, capable of inspecting the web at significantly higher web speeds, employs a parallel array of photodiodes positioned across the web. Each photodiode has its own threshold detector system and digital logic which allows a low-resolution defect size and position location characterization. The output signal can be processed to yield approximate size distribution and the location of the defects on the web.

The physical thickness of the web can be measured by a parallel array of web riders mounted in precision bearings. These rollers contact the web and are connected to transducers which electronically sense position to at least 1/10,000 inch. A similar system for the measurement of physical thickness can make use of pneumatic sensors which float above the web on a film of air of predetermined thickness. This system has the advantage of noncontact with the web.

Mass thickness (weight per unit area) or basis weight of the webs can be determined by using a noncontacting beta-ray or x-ray gauge. These systems measure the absorption of beta-rays or x-rays passing through the web. This absorption is related to mass thickness. In an alternative system, the electrical resistance between two contacting web-riding electrodes may be used to determine the basis weight of webs with known moisture content.

On-line analysis of moisture content can be measured by one or more of the following methods. First, the high dielectric constant of water allows sensitive moisture determination to be made by direct microwave absorption and by radio-frequency dielectric constant sensors. Low-frequenct conductance measurements can also be used to measure the amount of web moisture. Infrared spectrophotometric absorption provides a totally independent moisture measuring method. Further, the optical absorption at wavelengths in the region of 1-2 micrometers will yield a specific and precise moisture determination in a special region wherein the web being inspected is relatively transparent.

The web, having passed the inspection means 21, is guided by a suitable roller arrangement shown in Figure 2 to pass in close proximity to an active ingredient deposition apparatus 24 wherein active ingredient is loaded to the web. The deposition apparatus is immediately followed by means 25 schematically shown for on-line analysis/inspection, e.g. for content uniformity of active ingredient, of the coated web preferably as a single sheet before the active ingredient has been internalized.

A preferred method for the nondestructive on-line analysis of active ingredient deposited on webs is x-ray absorption. In this method, low energy x-rays peaked to match the absorption edge of atoms deposited on the web are directed through the coated web. The absorption of the x-rays is related to the active ingredient-plus-web absorption. Where the active ingredient is deposited on the web by a wet-coating process, this method of analysis may be utilized either before or after the drying step.

Since the total x-ray absorption arises from the combination of web and active ingredient

containing coating, it is necessary to determine the absorption of the web separately. This is accomplished by means of a beta-ray gauge or an infrared spectrophotometer. Increasing sensitivity is achieved for the x-ray measurement of deposited active ingredient containing atoms with increasing atomic numbers. The x-rays source can be tuned by varying the accelerating voltage to match the absorption edge for many atoms of interest.

Reflectance or transmittance spectrophotometry may also be utilized to nondestructively analyze the deposited active ingredient on-line. Reflectance spectrophotometry is used in the near ultraviolet region to determine active ingredient loading. This technique may be used with any solid active ingredient having an optical absorption in a suitable wavelength region.

Transmission spectrophotometry may also be used for nondestructive on-line analysis of active ingredient coated on webs. A suitable light source, monochromating element, and detector combination are selected for wavelength regions where the active ingredient selectivity absorbs. This must be in a spectral region where the web itself does not strongly absorb. Such regions for webs employed for the purposes of the present invention occur in the near-infrared and functional group infrared regions of the spectrum. A rapid wavelength scanning system is used to sweep over a small wavelength region of interest. The signal from the detector is time-averaged over several scans to reduce the effects of noise. The signal data are then processed to give a first derivative of transmission with respect to wavelength for increased sensitivity. This is done in a similar fashion for other wavelength regions which are sensitive to other components in the system. Thus water content, and basic weight of the web, as well as active ingredient content, can be determined simultaneously.

Another method for analysis of active ingredient loading is molecular fluorescence. Excitation radiation in the ultraviolet or visible region of the spectrum is provided by a suitable filter combination. The fluorescence from the active ingredient is detected by a wide-band filter-detector combination matching the fluoroscence peak; a blocking filter is used to remove the excitation energy. The detector for this method is preferably a photon counter, which counts individual photo events, providing high sensitivity and linearity at low levels of illumination. In this method of analysis, precautions must be taken to limit the photodegradation of the active ingredient by the excitation radiation.

The coated web may be stored for a time, or, preferably, directly forwarded to means for fabrication (block 16 of Figure 1) and unitizing (block 17 of Figure 1) to form dosage forms which means are illustrated in Figure 2 as a series of knives 26 for slicing the coated web into a multiplicity of endless strips, followed by fabricating and unitizing means 27 of the lamination type, i.e. the endless strips are stacked one on another to form an endless stack which is pressed and ultimately unitized in accordance with the invention as hereinafter described.

The unitized dosage forms are then finished and packed by appropriate apparatus (block 18 of Figure 1) schematically illustrated at 28 and 29 in Figure 2, for subsequent distribution. Appropriate inspection (at e.g. 30 in Figure 2) is performed in connection with this step. The purpose of the final inspection of individual dosage units is to verify size, shape, integrity, identity, presence and accuracy of printing, and active ingredient content. All of this inspection is done non-destructively except for active ingredient content. In order to analyze for active ingredient content and performance characteristics, a statistically appropriate sample of dosage units is removed from the production line and destructively analyzed both for potency and performance, e.g. dissolution characteristics, by solution spectrophotometry as will be discussed hereinafter.

An optical scanning system may be used to inspect all the production units for size, shape, integrity, identity, and the presence and accuracy of printing. The system can comprise a suitable light source and a matrix of photodetectors or a T.V. camera. A computer can be used to process the signals from the optical scanning system. Suitable algorithms are used to determine the acceptability of the dosage units. Another method employs a comparison of the sample image with a standard image by means of an image-masking technique.

In another method for 100% inspection, an optical transform of the image of the dosage unit is made. The Fourier transform spectrum, the power spectrum, or other suitable transform is compared with a similar transform of a standard by means of a computer.

Prior to the finishing step, and as indicated at 19 in Figure 1, an on-line analysis for dissolution and content uniformity can be performed by suitably arranged apparatus not particularly illustrated, which apparatus may include and/or be controlled by computer or similar central processing or logic means. A random sampling mechanism removes one dosage unit at a time from the end of the production line, usually at a rate of 25 to 120 units/min., preferably at a rate of 40-60 units/min. Each unit is sequentially transferred to a conventional automatic weighing device wherein it is weighed by nondestructive means and

the information stored. Randomly-selected units are then sequentially placed in a conventional automatic analyzing system. The dosage unit is stirred in a suitable solvent for the active ingredient at an appropriate rate. The amount of active ingredient dissolved at t_j minus the amount dissolved at t_i divided by t_j-t_i is taken as the rate of dissolution. The appropriate time interval (t_j-t_i) has been previously chosen and will vary with individual medicaments. A suitable time interval might range from 5 seconds to 2 minutes or more. The sample is then continuously stirred for a sufficient time to allow for all of the active ingredient to be dissolved, after which the solvent is analyzed for content of active ingredient. The amount of active ingredient in this analysis plus the amounts from samples t_i and t_j is the total present in the dosage form. This information is also recorded and stored. If the weight, thickness, dissolution rate, and analysis of the medicament content fall within previously defined limits, the units are deemed acceptable. If the readings do not fall within these limits, the units produced beginning with the negative analysis and ending with the next positive analysis are quarantined (i.e. segregated) for further evaluation.

It is to be noted in connection with Figure 1 that further provision is made for monitoring functions to be performed in accordance with this invention as are described hereinafter. Regarding the web inspection step (block 11), it is intended, for example, that continuous monitoring inspection of the web be made from the standpoint of the web color, thickness, continuity, soil spots and defects of virtually any kind. These functions may be performed by electronic and/or optical instruments as well as by visual observation.

Inspection of the web preferably includes the actual placing of a "flag" (i.e. a marker) on the web wherever a fault of defect is detected. Additionally, apparatus may be provided such that, whenever a defect is detected in the web, a printout is generated, either automatically or under operator control, indicating that on the web at certain distance downstream a defect of some sort exists, which printout would include an identification of the type of defect, such as a hole, blackspot, blemish etc..

The means for generating the printout can be the same apparatus actually flagging the web per se. Such apparatus is considered conventional in fabric manufacturing and fabric inspection, for example, and can be used here provided that the handling and inspection of the web would, in the instant case, be performed in accordance with good pharmaceutical manufacturing practices.

In addition, by the same or additional conventional inspection apparatus the web thickness would be measured. This could take the form of a visual display involving an operator or could be a detecting device coupled to a logic arrangement having upper and lower limits for web thickness, wherein if the thickness of the web violates one of the limits, there will also be effected a printout and a flag placed on the web as described above. One form of apparatus for providing thickness measuring of the web could take the form of an x-ray or a beta ray gauge or some similar device for measuring the mass thickness of the web.

In the case of block 13 of Figure 1, which relates to particle size reduction and flow control, it is intended that monitoring functions be performed as described in the following. In accordance with the invention, notwithstanding that the unloaded web itself has been monitored for defects and thickness, similar monitoring is contemplated following loading of the web with active ingredient(s). For example, x-ray gauge apparatus would, again, be applicable to determine the loaded web thickness, which thickness, in comparison to the earlier determined unloaded web thickness, would enable conclusions to be derived regarding the amount of active ingredient loaded to the web. Additionally, it is within the scope of this invention to provide actual mass monitoring means in order to determine the amount of active ingredient loaded to the web. It should be understood that performance of coated-web inspection could be effected by routing the coated web back through the same apparatus performing the web inspection represented by block 11 in Figure 1.

The active ingredient deposition system (block 14 in Figure 1) is preferably controlled by feedback from the on-line analysis of active ingredient content on the web. For example, electrical signals from the on-line analyzer (digital or analog) analyzing active ingredient loading (weight of active ingredient per unit area of coated web) are used in a feedback mode (reference 15 in Figure 1) to control the amount of active ingredient applied to the web in the deposition process. These feedback signals are fed, for example, to a minicomputer which produces a suitable correction signal for the deposition process. The correction signal causes either an increase or a decrease in the active ingredient loading so as to maintain the loading within a narrow range around the target value. For example, in a dry deposition process, in which the active ingredient powder is introduced into the deposition apparatus, the correction signal is used to control the feed rate and, consequently, the active ingredient loading.

In a wet deposition process, the correction signal may be utilized, for example, to vary the amount of the coating formulation which is applied to the web. For example, the gap

between metering rollers or between a metering knife and application roller is varied to change the active ingredient loading. In reverse roll coating, the rotational speed of the application roller is varied to change the active ingredient loading. Another means of control in wet deposition is by variation of the concentration of active ingredient in the coating liquid. Two liquid formulations containing different concentrations of active ingredient are preferably employed, these being mixed in the required proportions to supply the correct concentration; the ratio of the two formulations may then be varied to accurately control active ingredient loading.

Deposition of Medicament on the Web

The methods of "incorporating" active ingredient into the novel dosage forms of the present invention constitute a radical departure from methods of incorporating active ingredients into conventional solid dosage forms, e.g. tablets, capsules, dragees, suppositories, etc. While the methods and equipment utilized in the methods of the invention may vary somewhat, the overall prime object is uniformity of deposition, i.e. to deposit active ingredient on the moving web surfaces in an exceptionally uniform manner. The manner of active ingredient deposition utilized in accordance with the present invention is unique and possesses a number of advantages over manufacturing procedues commonly utilized in the pharmaceutical industry.

In view of the fact that the active ingredient is deposited on or substantially on the surface of an edible web which is then fabricated to completely internalize it, there is no need for common pharmaceutical excipients, fillers, preservatives and the like to be admixed with the active ingredient; thus we eliminate a cost and, more importantly, a source of potential incompatibilities and quality control problems. The web, in accordance with the present invention, is loaded with a uniform coating of active ingredient and is then divided into individual dosage forms by linear or geometric subdivision thereby effecting a level of uniformity of strength of active ingredient over a large number of dosage units which is substantially superior to the batch requirements now accepted in the pharmaceutical industry. In distinct contrast, conventional pharmaceutical manufacturing operations require that the active ingredients and suitable therapeutically inert pharmaceutical adjunct materials are prepared in a large quantity and subdivided volumetrically for filling into capsules or compression into tablets. Utilizing the manufacturing methods of the present invention, it is therefore possible to reduce the amount of excess active ingredient present to assure label dosage from the presently accepted level of from 5% to 10% by weight to approximately 1% to 5% by weight thereby realizing a substantial saving particularly when compounding very expensive active substances, e.g. certain hormones and antibiotics. Finally, the method of depositing or loading the active ingredient to the web in accordance with the present invention allows for continuous, on-line, non-destructive testing of the dosage by physical parameters, thereby facilitating the achievement of superior uniformity of amount of active ingredient over a large number of dosage forms.

The active ingredient may be loaded to the web in either wet or dry form, with dry form being preferred. In either instance, the active ingredient is deposited in a form susceptible to analysis as will be described hereinafter, i.e. a finely particulate form. The particle size is in the submicron range and can also be within a narrow size range from 1 up to 100 microns. Particles in the submicron range have heretofore been considered as being too fine for the production of pharmaceutical tablets without first being subjected to techniques such as granulation which substantially increases particle size and which also adds excipient matter to the active ingredient. The technology of the invention facilitates the use of such ultrafine particles without the need to resort to such techniques and/or the addition of excipient matter. The active ingredient is deposited as a very uniform coating on the web as it is being moved in an automated manufacturing system.

The preferred method of deposition of active ingredient on the web wherein the active ingredient is a dry form is powder cloud electrostatic deposition utilizing techniques generally recognized in certain non-pharmaceutical arts. Generally, this method requires passage of the web through an electrostatic field in a suitable chamber. Finely particulate active ingredient is introduced into the chamber via, for example, a forced air stream and is deposited on the web as it passes over an oppositely charged roller. It is readily apparent that this description is an oversimplification. However, apparatus effective to accomplish this result has been described in the literature of certain non-pharmaceutical fields such as the production of adhesives and adhesive papers. For a successful deposition to take place, it will be apparent that the web must have a resistivity capable of enabling the deposition thereon of dielectric particles. Additives which can be present in the web formulation to enhance the proper electrical properties thereof have been discussed above. In a number of instances, it has been found that, prior to electrostatic deposition of active ingredient powder, it is necessary to coat the web with a substance which will enhance the adherance

of the powder thereto. Examples of such substances include carboxymethylcellulose, methylcellulose and the like. These adherence enhancing substances may be applied to the webs in a conventional manner, e.g. by applying a solution in a fugitive solvent such as water and drying with, e.g. heated air. The application of a coating to the web to insure adherence of the active substance is then immediately followed on-line by the coating of "loading" of the web with active substance. The adhesive is then activated to bind the particles of active substance to the web. This is accomplished by applying heat, pressure, moisture or a suitable combination thereof to the loaded web. In addition to the eletrostatic powder cloud deposition method, one may use a method of coating fine particulate active ingredient onto the web in a dry state by electrogasdynamic powder coating. In this method, the particles of active ingredient are electrically charged by exposure to corona discharge and propelled by a gas stream into an electrically insulated chamber. The web is passed through this chamber on a metallic surface which is either grounded or charged with opposite polarity to that of the charged cloud of particles of active substances. The electric field between these particles and the metallic surface attracts them to the web and deposits them thereon.

Further in accordance with the present invention, active ingredient may be coated onto the web in the form of a solution or a suspension of finely divided medicament, i.e. a collodial suspension. The liquid utilized for these operations can be water, an organic solvent, e.g. ethanol, or a hydroalcoholic solvent. A preferred method of loading active ingredient in a liquid form onto a moving web is electrostatic jet spray deposition. In this method, the active ingredient containing solution or suspension is metered into an apparatus which projects a spray of microdroplets which are concentrated on a particular area of the web through the use of a defined-area electrostatic field. This method has given very good results where small quantities of active ingredients such as, for example, hormones or enzymes are to be loaded on the web. By small quantities we mean quantities of active substances having a usual dosage of less than one milligram.

In addition to electrostatic jet spray deposition, certain other coating techniques recognized in other arts as being amenable to the coating of a substrate with a liquid may be utilized in loading the web with active ingredient. For example, the paper web may be passed under a roll which is immersed in a bath of saturating fluid. As the web passes the roller, the excess fluid is "wiped" from the web by another roller, a jet of air, a rubber wiping bar, a wire-wound rod, i.e. a Meier rod, or the like. In this instance there is some penetration of the web by the solution, particularly if the solvent utilized to solubilize or suspend the active ingredient is the same as or similar to that utilized to form the paper web.

It will be appreciated that, while it is the object of the present invention to load the active ingredient to the surface of the web, some penetration of the web may result either from the use of a fugitive liquid carrier for the active ingredient or by the application of heat and/or pressure to the web to seal it. Simple preliminary experimentation with these factors, e.g. the use of fugitive liquids, will determine the percentage of active substance loaded to the web which may be absorbed therein. Once this parameter is established, the on-line testing apparatus as described herein can be adjusted accordingly. Where any appreciable amount of active substance is absorbed into the web, it is necessary to arrange for unloaded web, i.e. web without active ingredient, to form the outer surface of the dosage unit, thus preventing loss of active ingredient through exposure to deteriorating forces such as air and moistue. Obvious modifications of the fabricating processes to be described hereinafter will accomplish this result.

As stated above, one of the obvious advantages of the dosage forms of the present invention is that pharmaceutically active substance can be formulated into a stable dosage form without being admixed with conventional pharmaceutical excipients which are usually present in conventional solid dosage forms in quantities far exceeding the amount of active substance. It will be appreciated, however, that small amounts of inert substances may of necessity be loaded on to the webs with the active substance in accordance with the invention as described above. For example, where the active substance is loaded to the web in dry form, a small quantity, i.e. from about 0% by weight to about 10% by weight, preferably from about 1/4% by weight to about 2% by weight calculated on the weight of the active substance, of a glidant may be homogeneously admixed therewith. The purpose of the glidant is to facilitate the flow of the powdered active substance through the deposition apparatus. Suitable glidants include, for example, finely particulate siliceous preparations such as the colloidal silica marketed under the trademark Cab-O-Sil by the Cabot Corp., Boston, Mass., talc, finely particulte starch preparations, e.g. DriFlo marketed by National Starch, Inc., and the like. It can be appreciated that the inclusion of a glidant and the quantity thereof will depend on the crystalline structure and flow properties of the active substance. In certain instances, a preservative may be admixed with the active substance. However, where the active substance is loaded to the web in dry form, this is

technique should be amenable to high speed manufacturing operations and product a geometric form to exacting specifications of uniformity. The process must be capable of substantially internalizing the active substance. Finally, the fabrication or forming process must not put excessive stress on the webs so as to deform or tear them and must not dislodge a substantial quantity of active substance from the web. Each of the forming processes discussed hereinafter meets these criteria.

The first principal technique to be discussed concerns convolute winding of a moving web. It is perhaps appropriate to distinguish between convolute winding and spiral winding as recognized, for example, in the paper-converting industry. In spiral winding, the paper is fed to the spiral winding machine from several rolls where it is usually in coils that are 1/2 cm to 2 cm wide. The continuous strips of paper from each roll are coiled around a cylindrical mandrel which is supported at one end. The strips are coiled in such a way that they overlap. An adhesive is applied to each strip of paper and the overlapping strips from a continuous spiral as they are wound around the mandrel. The roll thus-formed is causes to rotate about the mandrel by the action of a continuous belt which also forces the paper roll forward toward the unsupported end of the mandrel. At the end of the mandrel, the tube thus-formed is cut into desired lengths by the intermittent action of a high-speed knife. Paper which is converted in this way would always have a hole in the middle by virtue of the mandrel upon which it is formed. In the convolute-winding process, there is no mandrel, and, therefore, it is not necessary nor desirable to have a hole in the center of the formed rod. In fact, it is expressly intended by this invention to make it possible to severely limit or eliminate altogether this central hollow area.

Reference is made to Figure 3 which diagrammatically illustrates one example of convolute winding. In the convolute winding process of Figure 3, the coated or loaded web 61 is fed from a single roll through a system comprising, for example, guide wires 62 and guide rollers 63, to a cutter arrangement 64 which cuts the web transversely into desired lengths, usually from about 12 cm to 25 cm in length. The sections of web are then guided into a corrugating roller arrangement 65 wherein a corrugating roller forms a series of creases by pushing the web against a soft rubber roller. As a result of the corrugating action, the individual sections of web are formed or curled into loosely would coils. The loosely curled webs emerging from the corrugating roller arrangement are then passed between a stationary surface and a moving surface, the space between the two surfaces being gradually decreasing along the course of travel of the curled webs. The stationary and moving surfaces may be in the form of two concentric cylinders, of which one is stationary and the other rotates relative to the stationary cylinder, or, as shown in Figure 3, they may be in the form of a flat fixed plate 67 as the stationary surface and a moving belt 66 as the non-stationary surface. As the sections of web as loosely wound rods pass between the moving and stationary surfaces, they are would tightly until a firm rod is formed. By appropriate adjustment of the spacing between the two surfaces, the rod can be wound tightly enough to eliminate any hole in the middle. It will, of course, be appreciated that, if desired, the spacing can be made so that a hole of desired size is left in the middle of the formed rod.

The rod can be sealed by several methods. First, it has been found that the conventional processes making, e.g. confectionery sticks are unacceptable in the practice of the present invention. In the conventional method the moving surfaces that come in contact with the web during rod formation are sprayed or coated with water to contact a large portion of the web. The amount of water absorbed by the web, about 18% by weight, is unacceptable for the preparation of the unit dosage forms of the invention due to possible effect on the adhesion of the medicament to the web as well as on the medicament itself. Further, the rods formed by this conventional process have been found for the most part to be too tightly sealed to give a good release of medicament in the body. It has been discovered in accordance with the present invention that spraying approximately the same portions of the web as in the conventional process with a sufficient amount of a fine spray of water to merely dampen it and rapidly drying the rods after formation yields final dosage forms possessing acceptable uniformity and rate of release of medicament as well as stability in terms of the active ingredient with the obvious exception of those medicaments which are recognized in the art of pharmaceutical compounding as being highly sensitive to the presence of moisture.

Second, the rods may be sealed by the application of a piece of heat-sealable edible polymer to the trailing edge of each sheet of web or the trailing edge of each sheet may be coated with a heat-sealable, edible polymer directly after the cut is made from the endless web. Alternatively, a heat-sealable polymer may be applied over the entire section of web either as a separate sheet or as a uniform coating. Suitable polymeric material would include, for example, a water-soluble polyoxyethylene or cellulose ether derivative containing a plasticizer such as is described above. After the rods are tightly wound, they

are in such an instance made to pass under a heated plate where both heat and pressure are applied to effect a seal. For example, a portion of fixed plate 67 could contain a heated section.

Alternatively, the rods, after formation, may be sealed by the application of water or an adhesive to the outer layer(s) or web. Preferably, water is used as the sealing agent. This method would usually require the presence of substances in or on the web composition, for example, starches or starch derivatives, which would form a seal through subsequent drying or with the application of heat and pressure.

The method illustrated in Figure 3, for purposes of example, provides for a water spray 68 to contact the outer surface of the endless belt 66 along the lower, return portion thereof, such that the belt surface contacted by the rolled web sections retains only enough water in the form of droplets to effect a proper seal of the rods. The water could also be applied to the tightly wound rods, for example by passing them under a water transfer roller, a porous plate through which a metered quantity of water is uniformly applied to the total length of the rods, or a sponge arranged water to the outer surfaces of the rods. The rods could then be caused to pass between a further section of the moving and stationary surfaces where pressure, or pressure and heat, may be applied to effect the completed seal.

This general method of effecting a water seal is deemed clearly superior to known methods of forming, for example, confectionery sticks as described above. With the water application methods as above-described the total amount of water applied to each rod is less than that applied by known methods. As a result, the amount of water to be removed during subsequent drying of the rods if substantially less than that generally required with known methods.

The rods thus-formed are each as long as the width of the web of the supply roll. This width is typically 20 to 40 cm. After each rod is sealed, it is caused to move into contact with, for example, ultrasharp knives 69 (Figure 3) by the belt 66, so that it is unitized, i.e. the rod is cut to desired lengths. Methods for unitizing and finishing these rods to final dosage forms are discussed below in further detail.

A second forming or fabrication method to be considered is generally identified as rotary forming. This method can take several specific forms. This method may be considered as being related to the more generic lamination method in that, in this method, stacks of web loaded withactive substance in endless strip or rod arrangements are initially prepared either by fan-folding or by lamination, both of which are discussed hereinafter. In one specific rotary forming method, as illustrated in Figure 4, a continuous, relatively thick laminated strap of web 70 loaded with active substance is passed between a pair of press rollers 71. The continuous thusly formed or pressed laminated stack 72 is fed to a second station, i.e. a rod shaping and densifying station, comprising, for example, one or more spring loaded stainless steel rollers 73 having a circumferential edge shaped to transform the strap into a plurality of continuous rods 74, or largely circular or other desired cross-section. The rods 74 shaped thereby into desired geometric form are than passed through a third rotary station comprising rollers 75, where, for example, one or more pairs of suitably arranged rollers 75 unitize the rods into individual doses. This may be followed by other suitable printing and finishing operations as are more particularly described hereinafter. It should be noted that the printing operation could be carried out in the unitizing step involving step involving the third set of rollers 75.

Another example of rotary forming is shown in Figure 5 wherein the formed endless stack (strip or rod) 81 is continously indented at regular intervals by reciprocating die blocks 82 and/or a pair of suitable heated rollers 83 to provide ultimately rounded corners in the final dosage units, such that the output of the rotary dosage forming station is a continuous chain or end-connected dosage units 85. As with all of the various methods of rotary forming according to the invention, the thusly altered rods can be passed through printing and rotary unitizing stations or subassemblies, e.g. as represented in Figure 5 by the rollers shown to the right of the rollers 83, all at high-speed.

The means delivering the intermediate product 81 in Figure 5 are (from left to right in Figure) active ingredient application units, single fold units, stacking rolls, and a rotary rod-forming unit.

In another closely related rotary forming technique, the continuous stack is fed into a rotary shaping and densifying assembly comprised as before of, for example, one or more pairs of stainless steel rollers. The layers of web, which may be made from layers of paper and polymer film, are heated and compressed into a continuous stack. It is preferably that the outer layers of the stack be paper, for example, to prevent sticking of the stack of the stack assembly to the heated rolls. During this densifying operation, the layers of web are bonded together as a unit, which reduces shifting of the layers and splitting of the edges during subsequent side- and end-forming operations. Next, the ends of the dosage units are formed by feeding the continuous rectangular stack produced at the densifying station into

a second station where the ends of the dosage units are formed by a pair of heated rollers which may have shaped, transversely-oriented cutters located on the rollers' faces. The cut ends of the dosage units are shaped and sealed by the heat from the rolls. The configuration of the end cutter determines the shape of the ends of the dosage units. The shape of the end cuts is designed to provide a smooth transition with the side cuts of the dosage units which are performed in the next station.

The sides of the dosage units are formed in the laminated end-formed, cut material stack with a third pair of heated rolls. These rolls may have angular grooves with raised cutting edges. The configuration of the grooves in the roll faces forms a desired dosage unit cross-section. Heat and pressure applied from the ridge-like cutting elements on the rolls seals the sides of the dosage units into a smooth surface.

A rotary-forming method of dosage unit fabrication basically as illustrated in Figure 5 may make use, therefore, of three primary stations, viz. a pre-densification station, and end-forming station, and a side-forming station. Each of these stations consists of a set of rollers, preferably heated, through which the continuous web stack is passed. The configuration of the outside surface, i.e. the face of the rollers at each of the stations is different, depending on the particular station and the result to be accomplished. Various additional operations, such as additional cutting, printing, or finishing steps can be performed between or at the three stations described. These operations are described further below.

It is to be noted that it is within the scope of this invention to perform one or more of the various steps in the rotary forming method simultaneously, and, in fact, perform on the endless laminate input strap, via a single pair of, for example, spring-loaded, heated cooperating rollers, all of the various above-discussed steps, i.e. rod-forming, dosage-forming, unitizing and even printing.

The above-described third example of rotary forming readily lends itself to an example of combining two or more of the outlined steps into one. Such combination is illustrated in Figure 4A wherein essentially the laminating press and rod-forming steps of the above-discussed third rotary forming method and also the method as illustrated in Figure 4 are combined, for example, through the use of a single pair of heated, pressing and cutting rollers (not particularly shown) which simultaneously press the laminate feed and end-cut it into a shape resembling a side view of a plurality of stacked doughnuts. These end-cut sections are then immediately fed to a unitizer which provides the longitudinal cuts enabling the individual dosages to be realized. The printing step, for example, could also be performed at this latter station. It is also within the concept of the present invention to package the unitized dosage forms directly as they come from the unitizing operation, for example, by inserting them into blister strips by apparatus considered conventional in the art.

A third method of forming dosage forms in accordance with the present invention is the fan-folding technique. One could also classify the fan-folding technique as being a form of lamination in a general sense. In this method, a web up to, for example, 30 cm wide is first fabricated to internalize the active ingredient loaded thereon. This may be accomplished either by initially folding the web in half or by laminating two coated webs with the coated surfaces facing. A stack of more than one pair of webs laminated in this manner may be utilized; the webs may initially be formed, for example, to a greater width, e.g. up to 60 cm, and, following lamination, divided to form two or more widths of a size convenient for the fan-folding operation, i.e. from about 1 cm to about 15 cm.

After the coated web has been initially folded or laminated as described above, it is then passed through scoring rolls where it is scored in preparation for the fan-folding operation. The scoring rolls may or may not be powdered. The web is basically moved by pulling rolls. Scoring can be accomplished, for example, by spring-loading one of the pair of scoring rolls. Since the web folds preferentially in the direction of the score rings which are impressed into the web material, the score rings may be positioned alternately in the upper and lower rolls in accordance with the desired fan-fold pattern. The scored web then passes into a fan-folding chute having folding blades which begin to gently bend the web at the point of contact and constrict both in width and overlap so that the web is reasonably tightly folded at the discharge end. At the end of the fold chute is a means for pulling the web through the scoring and folding apparatus such as, for example, a pair of stainless steel, spring-loaded driven rollers. This serves a dual function, i.e. the web is moved through the folding apparatus and the folded web is compacted into a continuous, solid geometric form. It is, of course, within the scope of this invention to combine the pulling means with means for sealing the web. However, the fan-folded web may be sealed by other methods as will be described hereinafter. The sealed webs may be unitized in a number of ways such as the rotary forming method described above.

In Figures 6A-6D one fan-folded dosage form technique is illustrated wherein initial

fan-folded webs 91 are assembled in perforations 92*a* of cooperating shape in a therapeutically inert web structure, preferably comprised of paper, identified as center strap 92. This "loaded" center strap bearing the fan-folded webs is then sandwiched between outer straps of web 93 to form a composite laminated structure. This composite endless laminated strap is then fed, in the direction shown by the arrow towards the right-hand side of Figure 6A, to, for example, a rotary dosage forming unit or station not unlike that of unit 83 of Figure 5, wherein the strap is caused to take onthe appearance of the continuous strip shown in Figure 6B. Finally, or simultaneously with the step performed in relation to Figure 6B, the unitizing step is performed, giving individual dosages such as the single dose illustrated in Figure 6C. Figure 6D illustrates in cross section, and on an enlarged scale, the dosage form illustrated in perspective in Figure 6C. Figure 6D shows how the fan-folded webs 91 are completely internalized and that, e.g. the center strap 92 is forced by the molding process outwardly somewhat, so that some of it is exposed between the edges of outer straps 93 which are sealed thereto. It should be noted that, preferably, outer straps 93 and center strap 92 are completely free of any active ingredient thereby ensuring that none of the active ingredients will be present on any exterior surface of the individual dosage forms.

The fourth principle forming method contemplated by this invention is the lamination method generally alluded to hereinbefore. In this method, between about 20 and 60 rolls of web are first simultaneously unwound from a multiple-reel unwind stand and then guided together to form a continuous rod. The 20 to 60 layers of web may all be paper-like material with an appropriate coating to facilitate sealing in a subsequent step, or they may be a laminate of a paper-like web and a heat-sealable, edible polymer web, or they may consist of one of more paper-like webs alternately interspersed with heat-sealable, edible polymer webs. Suitable polymeric materials include, for example, a water-soluble polyoxyethylene or cellulose ether derivative containing a plasticizer. Any number of the webs may be loaded with active substance. Preferably the paper composition webs are loaded with active substance.

An alternative method for stacking the webs which are loaded with active ingredient is to supply them directly from the deposition apparatus. The width of the web is usually 12 to 25 cm. The web, as stored on rolls or supplied from the deposition apparatus, may initially be a multiple of the final width which is slit to the final desired width as part of the stacking process.

Once the web is stacked, the continuous resultant bundle is guided to a lamination station. Apparatus known in diverse arts for bringing strips of flexible films together and forming a laminate therefrom is generally applicable to the practice of this embodiment of the present invention. As already discussed, the area of deposition of active substance on the web strips or sheets will vary depending, for example, on the method of sealing the lamination. The cutting and finishing of the laminate may likewise vary in accordance with the invention. For example, laminates can be treated as in the rotary forming process described above. However, the lamination station could also consist of a pair of reciprocating die plates which form, seal, and cut dosage forms from the continuously feeding web stack. A typical die plate would have a surface of approximately 25 cm x 25 cm.

The laminates formed in accordance with the present invention are, in a particular embodiment, unique in that they are sealed only at the edges as opposed to each sheet being totally sealed to the adjacent sheets. It has been found that, unexpectedly, suitable dosage forms can be produced from a stack of layers of web wherein up to six layers of paper composition web are interspersed between layers of a web comprised of a heat sealable polymeric composition by the application of heat and pressure to the stack by the cutting means during unitizing. During the unitizing operation, the layers of polymeric web in the stack become distorted by the heat and pressure and "spread" to cover and seal the edges of the intervening layers of paper composition. It is readily apparent that the top and bottom layers of such a laminate must be of polymeric composition. It is preferred that the medicament in a paper-polymeric web stack be loaded to the paper layers of web. It is readily apparent from the foregoing disclosure that such a laminate sealed only at the periphery possesses a superior rate of release of medicament than a similar stack of webs which has been totally laminated.

An alternative method for forming the dosages from the web stack is to pass the stack between rotating cylinders which have individual dual dies on the outer periphery. The dosage units are formed, sealed and cut from the continuously feeding web stack as it passes between such rotating cylinders.

Some pharmaceutical compounding benefits which are realized from the use of laminating techniques are herein considered. First, the laminating techniques provide barriers which facilitate the compounding of two or more therapeutically active substances which are incompatible, without the need to resort to the addition of stabilizing substances

or a special compounding technique such as, for example, encapsulation of one or more ingredients. Since up to, for example, 60 layers may be utilized to form a laminate, this embodiment of the invention is ideally suited for pharmaceutical preparations containing a large number of active substances where there are numerous possibilities of incompatibilities such as, for example, multivitamin preparations. Further, the insulating effect of layers of a laminate and the deposition or loading of active substance to the web in the dry state make such techniques ideally suitable for the dispensing of effervescent preparations. In such preparations, it is to be appreciated that the web composition would have to be such that it would readily dissolve or disperse in water. Also, as discussed above, loading of the active ingredient onto the web in the dry state inadvanageous where the active substance is adversely affected by moisture.

Further regarding the laminate process of the present invention, it is within the scope thereof to vary the formulation of the various layers within a laminate as well as to control whether each is coated with active substance. Obviously, the surface of the top and bottom layers of a laminate which will be exposed is not coated thus providing effective internalizing of the active substance. For example, it has been found that interspersing one or more layers of a starch-based formulation in a cellulosic laminate more expediently adds plasticity to the laminate then increasing the quantity of plasticizer in the formulation of the cellulose layers.

Regarding the method of forming discussed above, it is preferred in accordance with the invention to deposit or load the web with the active ingredient or ingredients in the wet form where forming is by the colvolute wind or fan-fold process. The rotary forming and lamination processes are equally amenable to deposition of active substance in wet or dry form with the choice being dependent on the characteristics of the active ingredient or ingredients being loaded, for example, solubility in the particular solvent being utilized, stability to moisture, and the like.

Unitizing

As a practical matter, unitizing cannot be discussed without also discussing sealing, and without first having discussed fabrication, since, by definition, cutting or unitizing the formed webs could expose some active ingredient at one or more of the outer surfaces. An exception to this would be possible by having the loading operation adapted to deposit active substance at short intervals, as opposed to a continuous deposition, thereby having active substance "spot deposited" and surrounded on all sides by uncoated web. In view of considerations of manufacturing equipment and the need to maintain the integrity of the deposition coating for on-line testing, it is preferred to load active substance continuously onto the web in sufficient amount so that the unitizing operation produces dosage forms containing a therapeutically efficacious dosage. In certain of the operations described herein, e.g. the fan-folding process, the outer margins of the web may be left free of active substance, to ensure internalizing of the active substance, and, in certain instances to provide excess web which can be utilized to seal the unitized dosage forms.

The cutting of the formed web must be accomplished in such a manner so as not to deform the web. The cutting operation itself may be accomplished by stationary or rotary knife blades, by single- or two-stage dies, or by other conventional methods. To ensure that the fabricated web will not be deformed during the cutting operation, several cuts may be made from different angles. Also, as discussed above with regard to rotary forming, the formed web can initially be crimped slightly or indented to compensate for the distortion caused by the high speed unitizing operation.

The formed, loaded web may be unitized by individual separation, i.e. the formation of one unit at a time as by cutting exact lengths from a rod or, preferably, a number of units may be formed simultaneously as by cutting a convolute wound rod into a number of dosage units utilizing a number of uniformity spaced cutting edges. Another method of forming a plurality of dosage units simultaneously would be the use of shaped dies, either single or double and rotary mounted, or reciprocally mounted on plates to cut a laminated web or a convolute would rod-like structure. The shape of the final dosage form preferably has cosmetic appeal and is such that a number of shapes will fit into a die plate with essentially no waste except at the periphery, as in the case of a rectangle, a square or, preferably, a hexagon.

The shape of the dosage forms prepared from rods can also be determined by the shape of the cutters. The cutters, for example could be of rectangular shape with the parallel larger sides moderately concaved so that the ends of the dosage forms cut therewith will be slightly rounded. Other variations will be apparent to those skilled in the art. It is to be borne in mind, however, that such lateral support as is required to prevent wrinkling and flashing must be applied to the fabricated dosage forms during the unitizing operation.

It is within the scope of the present invention to combine the unitizing and final sealing

operations. Although there are numerous ways by which the dosage forms can be sealed, the most commonly combined with the unitizing operation are heat and/or pressure. In addition to effecting a seal on the severed edges of the dosage form by heating the cutting tool, one can apply heat and pressure through the die to bond the laminate. Also, the use of moisture or a fugitive solvent to seal the trailing edge of a convolute wound rod as mentioned above can be extended to the cutting operation by applying such moisture or solvent to the cutting surface. Heat and/or pressure may also be applied at the same time to ensure a proper seal.

The methods whereby the unitizing dosage forms prepared in accordance with the present invention may be sealed are not unconventional in the plastics handling and laminating arts. These include, in addition to the use of water or other fugitive solvents such as, for example, ethanol, methanol and chloroform, the application of pressure and heat, the application of a separate adhesive, infrared heating, ultrasonic bonding, encapsulating or combinations of two or more of these. A preferred method of sealing dosage forms within the scope of the present invention is the use of an overwrap, which may be preprinted if desired. This overwrap may be, for example, a thin layer of edible polymeric material such as, hydroxymethyl cellulose, modified starch, and gelatin which is coated on to the dosage units in a bath into which the dosage units are immersed. Such layer could be self sealing as, for example, by removal of a fugitive solvent. More preferred methods of effecting a sealing layer on the unitized dosage units in accordance with the invention are encapsulation and basket sealing.

In the first of these methods, the solid dosage units are passed between converging layers of flexible film of, for example, gelatin which enclose the dosage form, e.g. as illustrated in Figure 6A. The gelatin film is then heat sealed and cut to shape. Apparatus for encapsulation of liquids by this method is accepted in the pharmaceutical industry, and such apparatus can readily be adapted to coat the novel dosage forms of the present invention.

A second method is basket sealing which may be accomplished by at least the following two processes. In the first, preformed baskets are prepared from material such as, for example, gelatin, or a cellulose derivative by apparatus well known, e.g. in the art of plastic molding, i.e. injection molding. The unitized dosage forms are placed automatically into these baskets at high speed and the baskets are then covered by an overlayer which is sealed to the basket by any of the sealing methods alluded to herein, preferably ultrasonic welding. The baskets are separated by cutting with a stationary or rotary cutting edge. The walls of the preformed basket are usually thicker than the top or sealing layer. The sealing layer, however, is sufficiently thick to protect the dosage form yet is such that the dosage form will be released from the basket via the sealing layer within a very short time after ingestion, usually within a few seconds after reaching the stomach. Alternatively, the basket may be formed from identical halves which are sealed by methods such as have been described herein.

An alternative to the basket seal described above is to form a continuous support web or strap of material such as described above for the basket, and cut holes therein to exactly accommodate the dosage form, e.g. fan-folded dosage forms as illustrated in Figure 6A. In this embodiment, the unitized dosage forms are placed into the holes, e.g. by the use of a first pin acting from below through the hole and a second pin on top of the unitized dosage form to keep it under compression. The strap is then sealed by the addition of a top and bottom layer of similar material while maintaining compression on the dosage units. The thickness of the strap is in no instance more than that of the dosage units. The strap, however, can be thinner than the dosage form but not less than approximately half the thickness thereof. It is preferred that the support strap to close to or equal to the thickness of the dosage form for a number of reasons. First, the sealing film can be as thin as that described above in connection with the basket since it is not significantly distorted in the sealing operation. Second, a thicker support web will be less subject to distortion during the perforating and unitizing operations. Third, holes can be made closer together in a thicker strap thus allowing for a minimum of waste. Once the dosage form has been placed in the support strap and sealed, the strap is again unitized as described herein. An advantage to both the basket and support strap concept described above is that there is web material on the outer surface which does not contain active substance and which could be subjected to finishing operations such as, for example, embossing, beveling, and the like without risk of loss of active substance. Also, the use of the basket or the support strap concept facilitate the use of varying colors in the final dosage form; for example, by making the support web, the sealing strips or the dosage units themselves in contrasting colors, an especially pleasing and distinctive appearance may be achieved.

The material to be utilized in preparing the basket, center support strap and sealing films described above must, as is the case with the webs themselves, meet critical tests. In addition to the obvious pharmaceutical criteria of being sufficiently pure, having good shelf

of active substance. For example, a photon counter can be utilized to measure ultraviolet absorption of the highly attenuating active substance-web system. Soft x-ray absorption utilizing radiation having a wavelength of about four Angstroms and beta-ray absorption can also be utilized. Light scattering apparatus is preferred since it is ideally suited for monitoring particle size and concentration in the powder cloud or on the web. The apparatus suitable for such operations is commercially available.

The fabrication, unitizing and finishing steps described above are likewise amenable to on-line testing procedures such as those described above in connection with the web. Such tests will, of course, involve physical parameters of the web after fabrication such as dimension, thickness, uniformity and the like. Similar tests are also carried out on the unitized dosage forms regarding shape, uniformity and the like.

The discussion to this point has centered on means whereby the novel dosage units of the invention are tested non-destructively on-line during production. Two additional tests are contemplated within the scope of the invention and without departing from the intended ambit of the terminology "non-destructive testing".

In the first such operation, a minute portion of the web is periodically removed on-line by cutting with knives, dies, fluid jets or a laser beam. It is contemplated that the portion of web removed will not destroy the integrity of the web of adversely affect any of the fabrication operations. The sample of the web can be removed before or after the active substance is loaded thereon or, in some instances, during early stages of fabrication, e.g. when a few webs have been stacked in a preliminary laminating or folding operation. The sample thus removed is chemically analyzed both for web composition and for active substance. This analysis is also carried out on a quantitative basis particularly with reference to active substance.

In addition to the spot analysis, the finished dosage forms are sampled and subjected to performance assurance on-line. While such testing is a procedure required at present with most solid dosage forms marketed in the United States it is not carried out on-line during the manufacturing operation as is the case with the present invention. First, it must be borne in mind that the novel dosage forms of the present invention are not encumbered by batch restrictions by virtue of the process whereby they are manufactured. A "batch" in accordance with the invention can therefore be the number of dosage units falling between two samples which meet the performance specifications provided that said number is not so high as to be incompatible with the sampling requirements of the Federal Food and Drug Administration. Since the sampling procedures contemplated in accordance with the invention substantially exceed the minimum entailed by such requirements, a "batch" of novel dosage units claimed herein can be any convenient number, e.g. the number of units which can be produced from a given production lot of active substance.

A second unique aspect of the performance assurance testing of the novel dosage forms of the subject invention is that the results of such tests, as well of those of all other on-line tests discussed herein, can be conputerized and utilized to adjust the parameters of the manufacturing process. By so doing, a negative reading on any of the tests signifies the beginning of a run of dosage units which must be isolated and the next following positive result after corrections are made automatically terminates the run which must be isolated. The dosage units produced between these two tests must then be further tested to determine how many conform to specifications. Where tests are being conducted on-line on the web, e.g. on the amount of active substance deposited, a negative reading can be automated to simultaneously actuate two functions. First, the web can be marked with a spot of non-toxic dye thus allowing for the production procedure to be temporarily halted and a section of web manually removed. Second, the reading, through a computer, actuates an adjustment in the amount of active substance being loaded onto the web to either increase or decrease said amount to conform to specifications. When the web passing the testing unit again conforms to specifications, a second spot will automatically be made on the web thus marking the length of web not meeting specifications. Similar operations are established at each of the on-line test sites.

Regarding the performance analysis operation, random samples of finished dosage units are removed and automatically deposited in aliquots of test solution and tested for dissolution rate. The particular criteria utilized to test for dissolution of the unit dosage forms will vary with the active substance or substances present therein. For example, a sample dosage unit can be added to a suitable solvent thereby forming a solution of the active ingredient. The resulting test solution can be photometrically scanned to record the concentration of active ingredient as a function of time after the test unit was inserted therein. Other possible indicators which could be measured in the test solution are changes in pH, color, heat, chemical reaction and the like. Means whereby each of these changes can be automatically recorded as a function of time are within the skill of those familiar with the art. Once the dissolution information is recorded, it can be utilized by a system such as a

computer to make such adjustments in the formation, unitizing, finishing and sealing operations as are required to correct or improve the readings.

The on-line testing procedures described herein are in all instances amenable to testing of the entire web, e.g. by means of a device which tests for web thickness. However, in certain instances testing of the entire web may not be feasible from the standpoint of economics. For example, it is possible to test a small area of web using a light scattering sensor and further possible to mount two or more sensing devices in close proximity to scan a corresponding number of small widths within a passing web. The cost of equipment required to have the total web scanned may, however, be prohibitive. Therefore, where only limited areas of the web can be checked, the testing equipment can be mounted on means which facilitate its oscillating across the width of the web. The percentage of web and therefore finished dosage units tested in this manner far exceeds the percentage tested in any non-destructive testing procedures peresently carried out in the pharmaceutical industry.

Finishing and Printing

As discussed at various points herein, the finishing operations for the novel dosage forms of the present invention may be conducted independently or, preferably, in combination with other operations, e.g. unitizing. Finishing, in the case of the novel dosage forms of the present invention, is divisible into two basic considerations, i.e. the uniformity of the surface of the dosage form and the finish or appearance of the surface thereof.

Uniformity of surface of the dosage forms of the invention may or may not be a problem depending on the technique employed to unitize the dosage forms from the continuous stack and whether a sealing operation is performed. For example, where a laminated stack of webs is cut to a particular shape as described above, a small flashing may be evident where the cutting means meet. Also, there may be some end or side flashing from the unitizing operation in dosage forms formed by other preferred methods of fabrication. Generally, however, the fabrication techniques of the present invention minimize the incidence of such flashing.

Flashing as described herein is generally removable by mild abrasion such as, for example, that produced by subjecting the dosage units to mild tumbling action with or without the presence of a mild abrasive substance such as salt crystals. It is to be understood that such action must, in most instances, precede printing operations.

The surface appearance, i.e. the gloss of the dosage forms of the present invention may vary from a mildly buffed appearance to reasonably high gloss depending on the technique utilized and the finish desired. Where sealing techniques such as, for example, the basket sealing or encapsulation methods referred to above are utilized, the gloss of the finished surface can be adjusted as desired by merely the selection of material utilized in forming the seal. The same is true where an overwrap is utilized to seal the dosage forms. Where such sealing operations are employed, complete removal of the flashing is usually not required since the overwrap assures complete continuity of surface.

The printing operation is likewise dependent on the fabrication and sealing techniques utilized. Printing may be effected on the web itself at any convenient point in the overall manufacturing operation. For example, the outer layer of a laminated dosage form may be printed prior to the fabrication operation, as part of the unitizing operation, or even after unitizing is completed. Dosage forms prepared by, e.g. convolute winding, can be printed while still in the continous rod or stack. Where the dosage forms of the invention are sealed by the application of an overwrap, printing is preferably carried out after the overwrap is applied although it is within the scope of the invention to print on the dosage form and apply a clear overwrap thereafter. The printing of solid unit dosage forms prior to completion of compounding thereof as is contemplated herein is a concept unique in the pharmaceutical industry.

The selection of a printing method is dependent on a variety of factors the most important of which is the physical nature of the substrate to be printed. The selection of an appropriate method is likewise dependent, to a degree, on the point in the overall manufacturing operation where printing is carried out, i.e. whether the web would be printed prior to fabrication, whether the finished dosage forms would be printed, or whether printing would be carried out at some intermediate point, perhaps in combination with other operations such as, for example, unitizing. The printing method and apparatus inherent thereto can be selected from the following: offset and direct letterpress; offset gravure; lithograph; electrostatic powder gravure; electrostatic screen stencil; ink jet and the like. Of these, offset gravure is the method of choice although other methods may be utilized in particular instances and such new methods of printing as come to hand and are adaptable to the technology described herein are considered to be within the scope of the invention.

It will be readily apparent from the foregoing discussion of finishing and printing

operations that there are a number of ways in which the color of the novel dosage forms of the present invention can be varied both in hue and intensity. First, the web composition itself can contain a color which can build in intensity as layers of web are joined during the various fabrication operations. The color may also be imparted by an overwrap or sealing layer. Where the basket or encapsulation methods of sealing are utilized, two or more contrasting colors may be possible by the obvious expedient of varying the color of the various sections thereof. The dosage forms prepared by lamination are also amenable to variations in color simply by varying the color of the webs fed into the laminating apparatus. Other variations of these techniques will be readily apparent to those skilled in the art.

Active Ingredient

The novel dosage forms of the present invention are, as a practical matter, unrestricted in terms of the type of active substance for which they can serve as a vehicle. The terms "active substance". "active ingredient" and "medicament", which are considered to be synonymous in the context of the subject invention and are utilized interchangeably throughout the instant description and claims, can be defined as including any substance which will produce a pharmacologic response in the body. Such substances include but are by no means intended to be restricted to the following:

The benzodiazephines such as, for example, chlordiazepoxide, diazepam, flurazepam, oxazepam, chlorozepate and the like. Additional compounds falling under the heating "benzodiazepines" are described in "The Benzodiazepines" Garattini, Mussini and Randal, Raven Press 1973 the disclosure of which it not intended as a limitation on the term;

Other tranquilizing agents such as, for example, reserpine, thiopropazate and phenothiazine compounds such as perphenazine, chloropromazine and the like;

Sedatives and hypnotics such as the phenobarbitals, methylprylon glutethimide, ethchlorvynol, methaqualone and the like;

Psychic energizers such as, for example, amitriptyline, imipramine, methylphenidate and the like;

Narcotic and non-narcotic analgesics such as codeine, levorphanol, morphine, propoxyphene, pentazocine and the like;

Analgesic - antipyretics such as, for example, aspirin, phenacetin, salicylamide and the like;

Anti-inflammatories such as, for example, hydrocortisone, dexamethazone, prednisolone, indomethacin, phenylbutazone and the like;

Antispasmodics/anticholinergics such as, for example, atropine, papaverine, propantheline, dicyclomine, clindinium and the like;

Antihistamine/antiallergenics such as, for example, diphenyldramine, chlorpheniramine, tripelennamine, brompheniramine and the like;

Decongestants such as, for example, phenylephrine, pseudoephedrine and the like;

Diuretics such as chlorothiazide, hydrochlorothiazide, flumethiazide, triamterene, spironolactone and the like;

Nutritional substances such as, for example, vitamins, essential amino acids and the like;

Anti-Parkinsonism agents such as, for example, L-DOPA alone and in combination with potentiators such as N^1-DL-Seryl-N^2-(2,3,4-trihydroxybenzyl) hydrazine;

Androgenic steroids such as, for example, methyltestosterone and fluoxymesterone;

Progestational agents such as, for example, progesterone, ethisterone, norethylnodrel, norethindrone, medroxyprogesterone and the like;

Estrogens such as, for example, estrone, ethinyl estradiol, diethyl stilbestrol and the like;

Hormonal preparations such as, for example, the prostaglandins, ACTH and the like;

Antibiotic/anti-infectives such as, for example, the penicillins, cephalophorins, tetracycline chlortetracycline, streptomycin, erythromycin, sulfonamides such as sulfisoxazole, sulfadimethoxine, sulfamethoxazole and other agents such as nitrofurazone, metronidazole and the like;

Cardiovascular agents such as, for example, nitroglycerin, pentaerythritol tetranitrate, isosorbid dinitrate, digitalis preparation, e.g. digoxin and the like;

Antacids/antiflatulents such, for example, aluminium hydroxide, magnesium carbonate, simethicone and the like;

Other therapeutic agents and/or combinations of agents such as are recognized in the medical arts as being therapeutically useful.

The active substances as utilized in the subject invention may be in the free form or in any non-toxic pharmaceutically acceptable form wherein their therapeutic activity is retained. For example, acidic substances may be present as esters or as salts with pharmaceutically acceptable inorganic bases such as for example, the sodium salt, the potassium salt and the like or organic bases such as amines or quaternary forms. Basic substances may be present

as salts with organic acids such as the acetate, the tartrate and the like. Certain substances such as, for example, ampicillin may be present in a hydrated form. In general, any pharmaceutically equivalent form of a given active substance which is recognized in the pharmaceutical compounding arts for said substance is utilizable in the dosage forms of the present invention provided, of course, that it does not exhibit incompatibility with the web substrate. In those few instances where such incompatibilities may exist, they are readily ascertained by simple experimentation.

The amount of the active substance or combination of substances to be incorporated into the novel dosage forms of the subject invention is usually that amount recognized as being an effective therapeutic dosage for the particular medicament. In general, the amount of active ingredient present in a single dosage form should not exceed about 500 mg with a practical upper limit being about 750 mg.

Dissolution

As stated herein, the novel dosage forms of the present invention possess an extremely consistent rate of release which is also controllable to meet desired specifications. Therefore, whatever pattern of release is contemplated, the dosage forms of the subject invention exhibit a consistency of rate of release within such pattern which is superior to that exhibited by conventional solid dosage forms, e.g. tablets and capsules.

Figure 7 is a graph which illustrates the superiority in release rate of the dosage forms of the invention in comparison with a conventional solid oral dosage form, i.e. commercial capsules. In the experiement whose results are illustrated in Figure 7, six randomly sampled conventional capsules each containing a like amount of the same active ingredient were each placed in 100 ml. of Artificial Gastric Fluid, U.S.P. (without enzyme). The fluid was maintained with stirring at 37°C. The fluid in each of the reaction flasks was constantly filtered and circulated through flow cells in an appropriate spectrophotometer.

The absorbance of the fluids was read at one minute intervals and the percentage of active ingredient dissolved calculated for each reading. In Figure 7 the fastest and slowest dissolving sample of each group are shown and the shaded area between covers the remaining four samples. The left-hand shaded area relates to the dosage forms of the invention, and the right-hand shaded area relates to the conventional capsules. From Figure 7, two conclusions are readily reached. First, the novel dosage forms of the subject invention dissolve much more rapidly than the conventional capsules tested. Second, the variation among six samples of the dosage units of the invention was strikingly less than that of the conventional capsules tested. These results clearly demonstrate the superior consistency of release which is characteristic of the dosage forms of the present invention.

The blood level curves depicted in Figure 8 also compare the novel dosage forms of the subject invention with commercially available capsules containing the same amount of the same active ingredient. The blood level curves are theoretically drawn based on two rates of input into a one-compartment pharmacokinetic model. The blood level curves are based on a theoretical 100% absorption of the amount of active ingredient released from the dosage form at a point in time and so are proportional to the dissolution rate. The difference in blood level curves is therefore a function of dissolution rates. The curve having a maximum above 7.0 micrograms/ml relates to the dosage forms of the invention and the curve having a maximum below 6.0 micrograms/ml, relates to the conventional capsules. The broken line at approximately 4.7 micrograms/ml shows the minimum effective concentration. It is clearly evident from the data illustrated in Figure 8 that the dosage forms of the subject invention not only reach effective blood levels more rapidly but attain a higher blood level of active ingredient than the conventional capsules. The ability to attain a higher blood level of active ingredient more rapidly is a distinct advantage particularly in the administration of certain types of chemotherapeutic agents, e.g. antiobiotics, cardiac active agents and the like.

WHAT WE CLAIM IS:

1. A solid pharmaceutical unit dosage form comprising a plurality of layers of an edible therapeutically inert web, at least one of said layers having a composition comprising one or more medicaments loaded to one or more surfaces, said layers of web being arranged so as to have substantially no medicament loaded to an outer surface thereof, said layered arrangement of web being sealed so as to completely internalize said medicament.

2. A unit dosage form according to claim 1, wherein said web is or a polymeric composition.

3. A unit dosage form according to claim 2, wherein said polymeric composition comprises an organic film forming ingredient and one or more plasticizers and optionally modifiers.

4. A unit dosage form according to claim 3, wherein natural or chemically modified starches or dextrins, proteins, cellulose derivatives, polysaccharides or synthetics are used

as organic film forming ingredient.

5. A unit dosage form according to claim 4, wherein gelatine is used as protein.

6. A unit dosage form according to claim 4, wherein sodium carboxymethylcellulose, hydroxypropylmethylcellulose or hydroxyethylcellulose is used as cellulose derivative.

7. A unit dosage form according to claim 4, wherein pectin, acacia, xanthin gum, guar gum or algin is used as polysaccharide.

8. A unit dosage form according to any one of claims 3 to 7, wherein the amount of film forming ingredient is from 5 to 95% by weight.

9. A unit dosage form according to claim 8, wherein the amount of film forming ingredient is from 40 to 90% by weight.

10. A unit dosage form according to claim 3, wherein glycerin, polysorbates or mixtures of mixed mono- and di-glycerides of saturated fatty acids are used as plasticizers.

11. A unit dosage form according to claim 10, wherein the amount of plasticizers is from 1 to 60% by weight.

12. A unit dosage form according to claim 11, wherein the amount of plasticizers is from 10 to 50% by weight.

13. A unit dosage form according to claim 3, wherein disintegrants, fillers and extenders are used as modifiers.

14. A unit dosage form according to claim 13, wherein various types of starches, casein or gelatin are used as disintegrants.

15. A unit dosage form according to claim 14, wherein the amount of disintegrant is up to 40% by weight.

16. A unit dosage form according to claim 15, wherein the amount of disintegrants is from 5 to 20% by weight.

17. A unit dosage form according to claim 13, wherein titanium dioxide, chalk, kaolin, mycrocrystalline cellulose or calcium carbonate are used as fillers or extenders.

18. A unit dosage form according to claim 1, wherein said web is of a paper composition.

19. A unit dosage form according to claim 18, wherein said paper composition comprises one or more fibrous materials and one or more non-fibrous modifiers.

20. A unit dosage form according to claim 19, wherein said paper composition comprises

a) from about 70% by weight to about 99% by weight of an edible fiber;

b) from about 1% by weight to about 30% by weight of an edible disintegrant selected from sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and guar gum;

c) from about 0% by weight to about 5% by weight of an edible surfactant.

21. A unit dosage form according to claim 20, wherein said ingredient a) is present in from about 90% by weight to about 96% by weight, said ingredient b) is present in from about 4% by weight to about 10% by weight and said ingredient c) is present in from about 0% by weight to about 2% by weight.

22. A unit dosage form according to claim 20, wherein said ingredient a) is comprised of edible hardwood fibers, edible softwood fibers or mixtures thereof.

23. A unit dosage form according to claim 20, wherein said ingredient b) is sodium carboxymethylcellulose.

24. A unit dosage form according to claim 20, wherein in the paper composition said ingredient c) is selected from the group consisting of polysorbate 80, sodium lauryl sulfate and dioctyl sodium sulfosuccinate.

25. A unit dosage form according to claim 20, wherein said paper composition additionally contains one or more edible, non-fibrous modifiers selected from edible fillers, extenders, opacifiers, electrolytes and preservatives.

26. A unit dosage form according to any one of claims 1 to 25, wherein the composition contains two or more medicaments.

27. A unit dosage form in accordance with claim 26 wherein said two or more medicaments are separated in said layered arrangement by at least one layer of web.

28. A unit dosage form in accordance with any one of claims 1 to 25 wherein said medicament is a benzodiazepine.

29. A unit dosage form in accordance with claim 27 wherein said medicament is chlordiazepoxide.

30. A unit dosage form in accordance with any one of claims 1 to 25 wherein said medicament is digoxin.

31. A unit dosage form according to any one of claims 1 to 30, wherein said layered arrangement of web is a laminate.

32. A unit dosage form according to any one of claims 1 to 30 wherein said layered arrangement of web is a wound roll.

33. A unit dosage form in according to any one of claims 1 to 30 wherein said layered arrangement of web is a fan-folded arrangement.

34. A unit dosage form according to any one of claims 1 to 25, wherein the layers of web are arranged in a stack wherein substantially no medicament is loaded to an outer surface thereof, said stack of webs being sealed at the edges so as to completely internalize said medicament.

35. A unit dosage form according to claim 34 wherein at least two layers in said stack of webs consist of a heat sealable polymeric composition comprising an organic film-forming ingredient and a plasticizer therefor and at least one layer in said stack of webs consists of a paper composition comprising one or more fibrous materials and at least one non-fibrous modifier therefor, the top and bottom layers of said stack being polymeric with the proviso that there be no more than six of said paper composition webs interspersed between each pair of said polymer composition webs in said stack.

36. A unit dosage form according to claim 35 wherein said non-fibrous modifier in said paper composition comprises an organic film-forming ingredient.

37. A unit dosage form according to claim 36 wherein said film-forming ingredient in said polymeric composition and said paper composition is selected from hydroxypropylcellulose and sodium carboxymethylcellulose.

38. A method of preparing solid pharmaceutical unit dosage forms comprising loading one or more medicaments to a therapeutically inert, edible web, fabricating same into a solid geometric form of predetermined shape having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms, and unitizing said geometric form into said plurality of unit dosage forms and sealing unit dosage forms to completely internalize said medicament; with or without at least one non-destructive testing operation to assure uniform quality of said unit dosage forms.

39. A method in accordance with claim 38 wherein said method is carried out in a substantially continuous manner by way of automated apparatus.

40. A method in accordance with claim 38 wherein said fabricating step comprises laminating a plurality of layers of web and said unitizing procedure comprises simultaneously cutting a plurality of unit dosage forms of predetermined shape from said laminate.

41. A method in accordance with claim 40 wherein from about 20 to about 60 layers of said web are utilized to form said laminate.

42. A method in accordance with claim 40 wherein said dosage units are sealed by applying heat to the edges thereof during said cutting step to effectively seal same.

43. A method in accordance with claim 40 wherein said unit dosage forms are sealed by coating them with an edible, therapeutically inert polymeric material.

44. A method in accordance with claim 41 wherein at least one of said plurality of layers of web forming said laminate is free of medicament.

45. A method in accordance with claim 41 wherein at least two of said layers of web are loaded with different medicaments, and said layers loaded with different medicaments are arranged in said laminate so that at least one layer of web is transposed so as to separate all such different medicaments.

46. A method in accordance with claim 39 wherein said medicament is loaded to said web in dry form.

47. A method in accordance with claim 46 wherein said medicament is uniformly admixed with a therapeutically inert, edible glidant material.

48. A method in accordance with claim 38 wherein said medicament is loaded to said web by powder cloud electrostatic deposition.

49. A method in accordance with claim 39 wherein said medicament is loaded to said web by applying a solution or dispersion of said medicament in a suitable liquid and thereafter removing said liquid.

50. A method in accordance with claim 49 wherein medicament containing solution or dispersion is applied to the web by electrostatic jet spray deposition.

51. A method in accordance with claim 39 wherein a non-destructive testing operation is included which comprises monitoring the particle size and concentration of medicament on the loaded web by way of light scattering techniques.

52. A method in accordance with claim 38 wherein said fabrication procedure comprises cutting said loaded web transversely to form substantially uniform lengths of loaded web each divisible into a plurality of unit dosage forms, corrugating each length of web to form same into a loosely wound coil, convolute winding said loose coils to form a substantially solid rod and cutting said rod transversely to form a plurality of unit dosage forms.

53. A method according to claims 38 and 52, wherein a web is used having a composition that is amenable to being watersealed and wherein the rods are sealed by contacting the coils with a sufficient amount of water as a fine spray to dampen them and

subsequently drying the rods.

54. A method according to claims 38, 52 and 53, wherein the application of water is limited to the point on the surface of said rod wherein the seal is required.

55. A method according to claim 38, which comprises forming a stack of said webs at least one of which has medicament loaded thereto, cutting said stack to unitize same into unit dosage forms and simultaneously applying heat and pressure during said cutting procedure to seal only the edges of said unit dosage forms thereby completely internalizing said medicament, said procedure including at least one non-destructive testing operation to assure uniform quality of said unit dosage forms.

56. A method in accordance with claim 55 whereinsaid stack of webs comprises at least two layers of web consisting of a heat sealable polymeric composition comprising an organic film-forming ingredient and a plasticizer therefor and at least one layer of a paper composition comprising one or more fibrous materials and at least one non-fibrous modifier therefor, the top and bottom layers of said stack being polymeric with the proviso that there be no more than six of said paper composition webs interspersed between each pair of said polymer composition webs in said stack and said heat and pressure applied to said stack of webs during said cutting operation is sufficient to cause said polymeric webs to deform and seal the edges of any intervening layers of paper composition webs.

57. A method according to claim 38 which comprises forming a continuous stack of a plurality of layers of web and subjecting said stack to pressure to densify and shape into a continuous rod-like first geometric form, unitizing said geometric form into said plurality of unit dosage forms and sealing said unit dosage forms to completely internalize said medicament, said procedures including at least one non-destructive testing operation to assure uniform quality of said unit dosage forms.

58. A method in accordance with claim 57 wherein said unitizing step comprises uniformly transversely identing said rod-like first geometric form and thereafter severing said geometric form at said indentations to form dosage units.

59. A method in accordance with claim 57 wherein said unitizing step comprises longitudinally cutting said rod-like first geometric form to yield a plurality of continuous geometric forms each divisible into a multiplicity of dosage units and thereafter transversely cutting each of said plurality of continuous geometric forms at uniform intervals to form individual dosage units.

60. A method in accordance with claim 57 wherein said unitizing step comprises transversely cutting said rod-like first geometric form at uniform intervals to yield a plurality of geometric forms each divisible into a plurality of dosage units and thereafter longitudinally cutting said forms to form individual dosage units.

61. A method in accordance with claim 57 wherein said continuous stack of a plurality of layers of web is formed by laminating a plurality of webs arranged to have the top and bottom surface free of medicament.

62. A method according to claim 38 for forming edible webs suitable for the production of solid pharmaceutical unit dosage forms comprising forming a paper web from a first composition comprising from about 70% by weight to about 99% by weight of an edible fiber in a suitable fugitive liquid and, prior to removing said liquid, adding to said web a second composition comprising a solution of from about 1% by weight to about 30% by weight of an edible disintegrant selected from sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and guar gum and from about 0% by weight to about 5% by weight of an edible surfactant in a suitable liquid and thereafter removing said liquids, said percentages by weight being of the finished web composition.

63. A method in accordance with claim 62 wherein said first composition comprises from about 90% by weight to about 96% by weight of said fiber and said second composition comprises a solution of from about 4% by weight to about 10% by weight of said edible disintegrant and from about 0% by weight to about 2% by weight of said edible surfactant.

64. A method in accordance with claim 62 wherein the liquids in said first and said second compositions are the same.

65. A method according to claim 38 for preparing solid pharmaceutical unit dosage forms comprising loading one or more medicaments to a therapeutically inert, edible web, fabricating said web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms, unitizing said geometric form into said plurality of unit dosage forms and sealing said unit dosage forms to completely internalize said medicament wherein said procedures include at least one non-destructive testing operation to assure uniform quality of said unit dosage forms, wherein said fabrication procedure comprises fan folding a continuous web structure with the formation of a stack comprising at least one pair of layers of web having medicament loaded to the facing surfaces thereof and subjecting said stack to

pressure to densify and shape same into a continuous rod-like geometric form.

66. A method in accordance with claim 65 wherein said unit dosage forms are sealed and unitized by:

a) placing them in perforations of cooperating shape within an endless web strap comprised of therapeutically inert, edible material;

b) placing said web strap between two endless webs comprised of therapeutically inert, edible material and sealing said webs to said unit dosage form-containing strap thereby forming a sandwich structure completely internalizing said unit dosage forms; and

c) transversely cutting said sandwich structure between said perforations of said perforated strap such that exposure of any part of said unit dosage forms is avoided.

67. A method in accordance with claim 66 wherein said strap has a thickness equal to or greater than x and not greater than y wherein x is approximately one half of the thickness of said unit dosage forms and y is approximately the thickness of said unit dosage forms.

68. A method in accordance with claim 65 wherein said unit dosage forms are sealed and unitized by:

a) placing them in perforations of cooperating shape within an endless web strap comprised of therapeutically inert, edible material, which endless perforated strap is secured initially to a first endless unperforated web comprised of therapeutically inert, edible material of comparable dimensions to said perforated web strap so as to form said perforations into bottomed receptacles for receiving said unit dosage forms.

b) covering the open portion of said receptacles with a portion of a second endless unperforated web comprised of therapeutically inert, edible material;

c) sealing said second web to said receptacles thereby completely internalizing said unit dosage forms; and

d) transversely cutting said sealed strap between said perforations such that exposure of any part of said unit dosage forms is avoided.

69. A method according to claim 38 for preparing solid pharmaceutical unit dosage forms comprising loading one or more medicaments to a therapeutically inert, edible web, fabricating said web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms, unitizing said geometric form into said pluraity of unit dosage forms and sealing said unit dosage forms to completely internalize said medicament wherein said procedures include at least one non-destructive testing operation to assure quality of said unit dosage forms, said method further including printing of appropriate indicia on said unit dosage forms, wherein said printing is carried out prior to the completion of sealing said unit dosage forms.

70. A method in accordance with claim 69 wherein said printing is carried out on said webs prior to said loading of medicaments thereto.

71. A method in accordance with claim 69 wherein said printing is carried out simultaneously with said unitizing procedure.

72. A method in accordance with claim 69 wherein said printing is carried out simultaneously with said sealing procedure.

73. A method according to claim 38 for preparing solid pharmaceutical unit dosage forms comprising loading one or more medicaments to a therapeutically inert, edible web, fabricating said web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms, unitizing said geometric form into said plurality of unit dosage forms and sealing said unit dosage forms to completely internalize said medicament wherein said procedures include at least one non-destructive testing operation to assure uniform quality of said unit dosage forms, the said at least one testing operation being or including an on-line non-destructive testing operation which comprises evaluating and quantifying the uncoated web for physical integrity.

74. A method in accordance with claim 73 wherein said evaluating and quantifying include impinging monochromatic light energy onto the web and photodetecting said light energy recovered from the web in a transmissive mode.

75. A method in accordance with claim 73 wherein said evaluating and quantifying include impinging monochromatic light energy onto the web and photodetecting said light energy recovered from the web in a reflective mode.

76. A method in accordance with claim 75 wherein said impinging energy is electronically steered across the web.

77. A method in accordance with claim 73 wherein said evaluation and quantifying include providing an electrical output for cunting the number of defects and determining their size and distribution on the web.

78. A method in accordance with claim 76 wherein said evaluating and quantifying include providing high speed parallel array inspection transverse to the relative direction

of movement of the web.

79. A method according to claim 38 for preparing solid pharmaceutical unit dosage forms comprising loading one or more medicaments to a therapeutically inert, edible web, fabricating said web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms, unitizing said geometric form into said plurality of unit dosage forms and sealing said unit dosage forms to completely internalize said medicament wherein said procedures include at least one non-destructive testing operation to assure uniform quality of said unit dosage forms, the said at least one testing operation being or including an on-line non-destructive testing operation which comprises measuring the mass thickness of said web prior to and after the loading of said medicament by determining the absorption of beta-rays or x-rays passing through the web.

80. A method in accordance with claim 79 wherein said determination of absorption occurs after said medicament is loaded to said web and includes directing through the loaded web low energy x-rays peaked to match the absorption edge of atoms contained in the medicament.

81. A method in accordance with claim 80 wherein said medicament is loaded to said web as a solution or dispersion in a suitable liquid which liquid is subsequently removed and wherein said determination of absorption occurs before or after the removal of said liquid.

82. A method according to claim 38 for preparing solid pharmaceutical unit dosage forms comprising loading one or more medicaments to a therapeutically inert, edible web, fabricating said web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms, unitizing said geometric form into said plurality of unit dosage forms and sealing said unit dosage forms to completely internalize said medicament wherein said procedures include at least one non-destructive testing operation to assure uniform quality of said unit dosage forms, the said at least one testing operation being or including an on-line non-destructive testing operation which comprises determining the concentration of the medicament loaded to said web by molecular fluorescence or x-ray fluorescence.

83. A method according to any one of claims 38-82, applied to the manufacture of an unit dosage according to any one of claims 1 to 37.

84. Unit dosage form according to any one of claims 1 to 37 whenever manufactured by a method according to any one of claims 38 to 82.

85. A system for producing solid, pharmaceutical unit dosage forms comprising in combination:

a) first means for producing a web of edible, therapeutically inert material;
b) second means receiving said web for loading to said web at least one medicament;
c) third means receiving said loaded web for fabricating said loaded web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms;
d) fourth means receiving said geometric form for unitizing said geometric form into a plurality of unit dosage forms;
e) fifth means receiving said unit dosage forms for sealing said unit dosage forms and completely internalizing said medicament; and
f) means for the on-line non-destructive testing of the output of at least one of said first, second, third, fourth and fifth means, whereby uniform quality of said unit dosage forms is ensured.

86. A system in accordance with claim 85 wherein said third means includes means for stacking a plurality of layers of web and means for laminating said stack into a solid geometric form and said fourth means includes means to form a plurality of unit dosage forms of pre-determined shape simultaneously from said laminate.

87. A system in accordance with claim 85 wherein said fourth means and said fifth means constitutes an integral device performing both unitizing and sealing substantially simultaneously.

88. A system in accordance with claim 87 wherein said fifth means includes means to apply heat to the edges of the dosage forms during said cutting step.

89. A system in accordance with claim 85 wherein said second means includes means for loading said medicament in dry form.

90. A system in accordance with claim 89 wherein said means includes powder cloud electrostatic deposition means.

91. A system in accordance with claim 85 wherein said second means includes means for applying a solution or dispersion of said medicament in a suitable liquid to said web and means for removing said liquid.

92. A system in accordance with claim 91 wherein said applying means includes electrostatic jet spray deposition means.

completely internalizing said medicament; and

f) means for testing on-line non-destructively the output of at least one of said first, second, third, fourth and fifth means, and thereby ensuring uniform quality of said unit dosage forms.

101. A system in accordance with claim 100 wherein said fourth means includes means for uniformly transversely indenting said first means geometric form and means for severing said first geometric form at said indentations to form dosage units.

102. A system in accordance with claim 100 wherein said fourth means includes means for longitudinally cutting said first geometric form to yield a plurality of continuous geometric forms each divisible into a multiplicity of dosage units and means for transversely cutting each of said plurality of continuous geometric forms at uniform intervals to form individual dosage units.

103. A system in accordance with claim 100 wherein said fourth means includes means for transversely cutting said first geometric form at uniform intervals to form a plurality of geometric forms, each divisible into a plurality of dosage units, and means for longitudinally cutting said forms to form individual dosage units.

104. A system in accordance with claim 100 wherein said means for forming a continuous stack of plurality of layers of web includes means for laminating said layers of web.

105. A system for producing solid, pharmaceutical unit dosage forms comprising in combination:

a) first means for producing a web of edible, therapeutically inert material;

b) second means receiving said web for loading to said web at least one medicament;

c) third means receiving said loaded web for fabricating said loaded web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms, said means including means for forming a continuous stack of a plurality of layers of web by fan-folding a continuous structure comprising at least one pair of layers of web having medicament loaded to the facing surfaces thereof, and means for densifying and shaping said stack into a continuous rod-like geometric form;

d) fourth means receiving said geometric form for unitizing said geometric form into a plurality of unit dosage forms;

e) fifth means receiving said unit dosage forms for sealing said unit dosage forms and completely internalizing said medicament; and

f) means for testing on-line non-destructively the output of at least one of said first, second, third, fourth and fifth means, and thereby ensuring uniform quality of said unit dosage forms.

106. A system in accordance with claim 105 wherein said fabrication means includes means for forming said continuous web structure by folding a web loaded with medicament on one side so that said medicament is internalized.

107. A system in accordance with claim 105 wherein said fabrication means includes means for forming said continuous web structure by laminating at least one pair of layers of web loaded on one side with medicament arranged so that their loaded surfaces are facing.

108. A system in accordance with claim 105 wherein said fifth means includes:

a) means for placing said unit dosage forms in perforations of cooperating shape in an endless, web strap of edible material;

b) means for placing said strap between two endless webs comprised of edible material thereby forming a sandwich structure;

c) means for sealing said sandwich structure thereby completely internalizing said unit dosage forms; and

d) means for cutting said sandwich structure between said perforations of said perforated strap, whereby exposure of any part of said unit dosage forms is avoided.

109. A system for producing solid, pharmaceutical unit dosage forms comprising in combination:

a) first means for producing a web of edible, therapeutically inert material;

b) second means receiving said web for loading to said web at least one medicament;

c) third means receiving said loaded web for fabricating said loaded web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms;

d) fourth means receiving said geometric form for unitizing said geometric form into a plurality of unit dosage forms;

e) fifth means receiving said unit dosage forms for sealing said unit dosage forms and completely internalizing said medicament; and

f) means for testing on-line non-destructively the output of at least one of said first, second, third, fourth and fifth means, and thereby ensuring uniform quality of said

unit dosage forms
wherein said testing means comprises sixth means for evaluating and quantifying the physical integrity of the uncoated web, said sixth means including monochromatic narrow beam light generating means arranged to continuously illuminate said web in a predetermined manner with light energy, electronic control means for controlling said light generating means and photodetecting means arranged to receive said light energy recovered from the web.

110. A system in accordance with claim 109 wherein said sixth means further includes means coupled to said photodetector means for cutting the number of web defects, and for determining the size and distribution thereof.

111. A system in accordance with claim 109 wherein said photodetecting means comprises a parallel array of photodetecting devices arranged transverse to the direction of movement of said web, each said photodetecting device having associated therewith thereshold means and digital logic means.

112. A system for producing solid, pharmaceutical unit dosage forms comprising in combination;

a) first means for producing a web of edible, therapeutically inert material;
b) second means receiving said web for loading to said web at least one medicament;
c) third means receiving said loaded web for fabricating said loaded web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms;
d) fourth means receiving said geometric form for unitizing said geometric form into a plurality of unit dosage forms;
e) fifth means receiving said unit dosage forms for sealing said unit dosage forms and completely internalizing said medicament; and
f) means for testing on-line non-destructively the output of at least one of said first, second, third, fourth and fifth means, and thereby ensuring uniform quality of said unit dosage forms.

wherein said testing means comprises seventh means for determining the thickness of the web before and after loading of the medicament thereto.

113. A system in accordance with claim 112 wherein said seventh means includes, in the instance of testing for physical thickness, a parallel array of web rider means mounted transverse to the direction of movement of said web and in contact therewith, and a plurality of transducers in one-to-one correspondence with said web rider means for continuously electronically sensing the position of said rider means.

114. A system in accordance with claim 112 wherein said seventh means includes, in the instance of testing for mass thickness, means for generating beta-ray or x-ray energy for impingement on the web, and beta-ray or x-ray gauge means arranged relative to said web and to said impinging energy for measuring the absorption of said energy by said web.

115. A system for producing solid, pharmaceutical unit dosage forms comprising in combination:

a) first means for producing a web of edible, therapeutically inert material;
b) second means receiving said web for loading to said web at least one medicament;
c) third means receiving said loaded web for fabricating said loaded web into a solid geometric form of predetermined dimensions having said medicament substantially internalized, said form being divisible into a plurality of unit dosage forms;
d) fourth means receiving said geometric form for unitizing said geometric form into a plurality of unit dosage forms;
e) fifth means receiving said unit dosage forms for sealing said unit dosage forms and completely internalizing said medicament; and
f) means for testing on-line non-destructively the output of at least one of said first, second, third fourth and fifth means, and thereby ensuring uniform quality of said unit dosage forms

wherein said testing means comprises eighth means for determining the concentration of medicament loaded to the web, said eighth means including means for providing excitation radiation in the ultraviolet or visible region of the spectrum for impingement on the loaded web, and means for detecting the fluorescence from said medicament.

116. A system according to any one of claims 85-115, applied to a method according to

any one of claims 38-83 and to the preparation of an unit dosage form according to any one of claims 1 to 37.

117. A unit dosage form according to any one of claims 1 to 37, as hereinbefore particularly described.

118. A method for preparing an unit dosage form according to any one of claims 38 to 83, as hereinbefore particularly described.

119. A system for preparing an unit dosage form according to any one of claims 85 to 115, as hereinbefore particularly described.

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Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1980.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

1561100 COMPLETE SPECIFICATION
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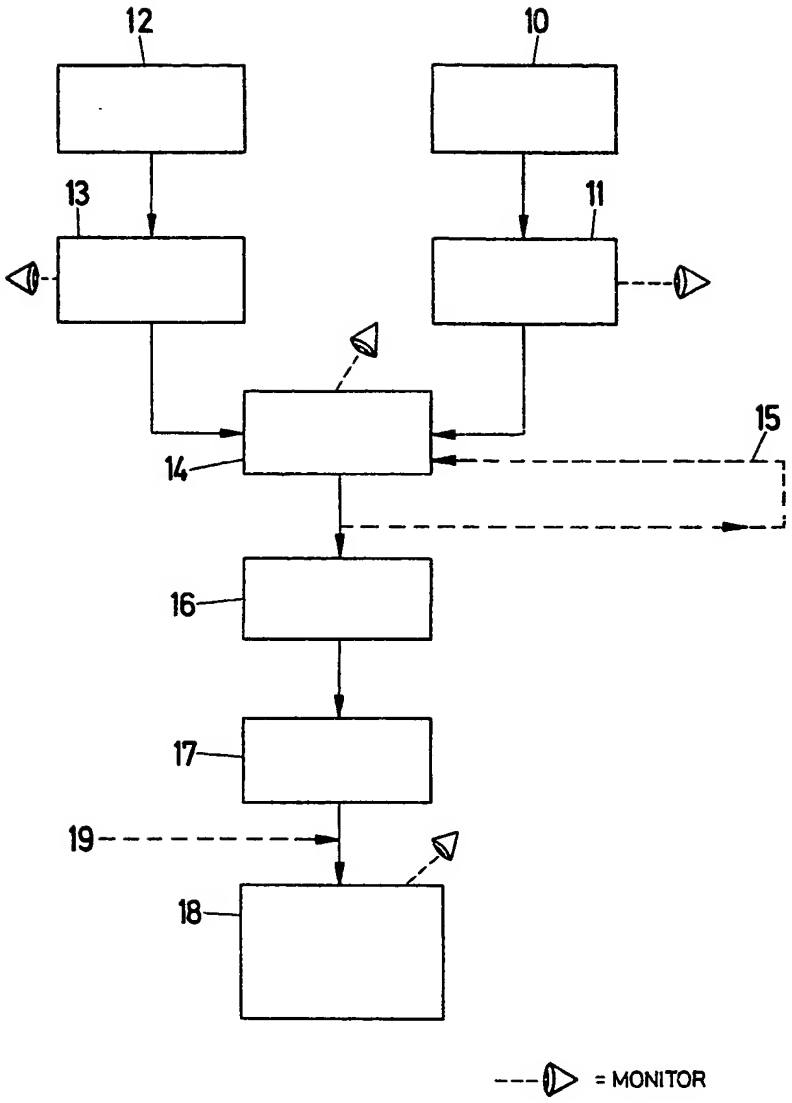


FIG.1

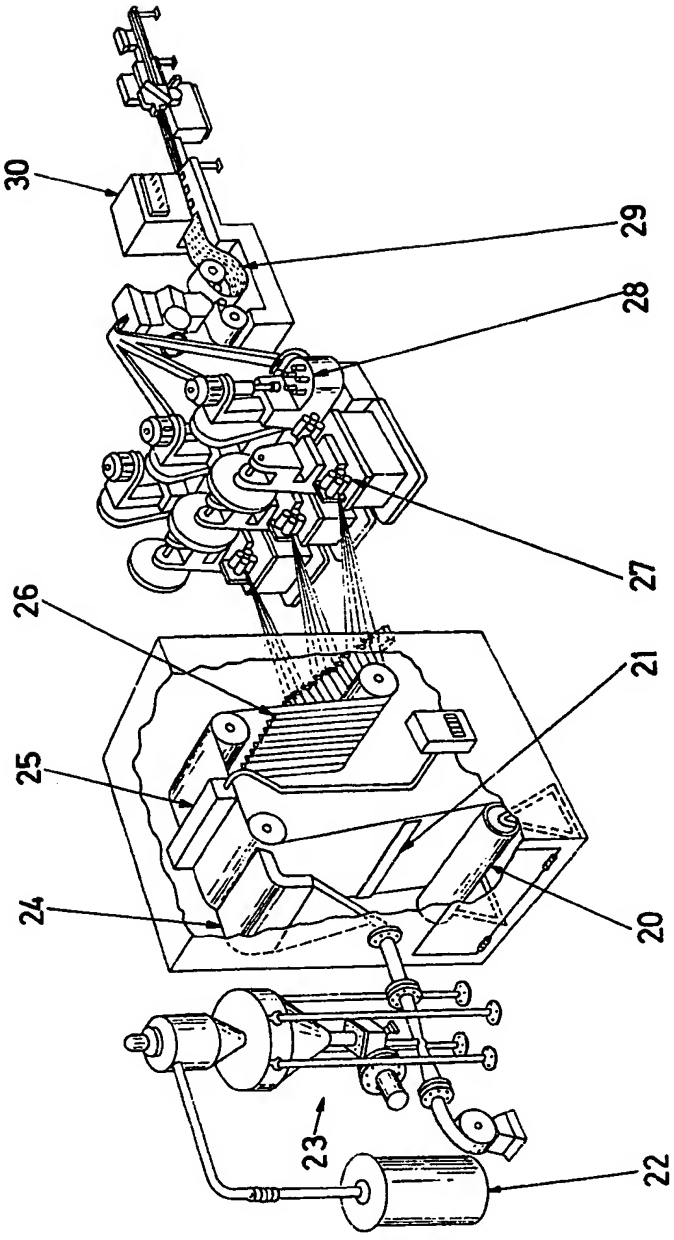


FIG.2

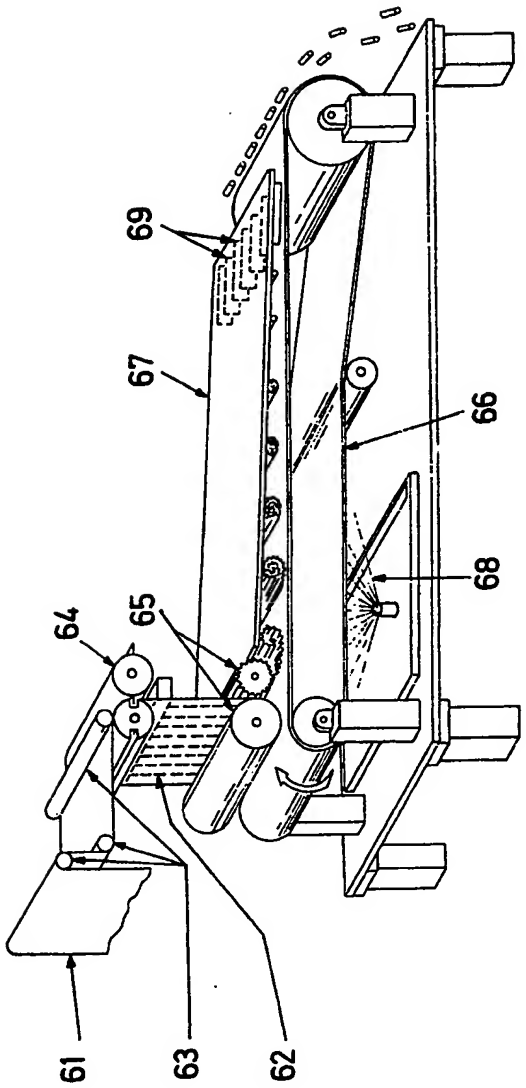


FIG.3

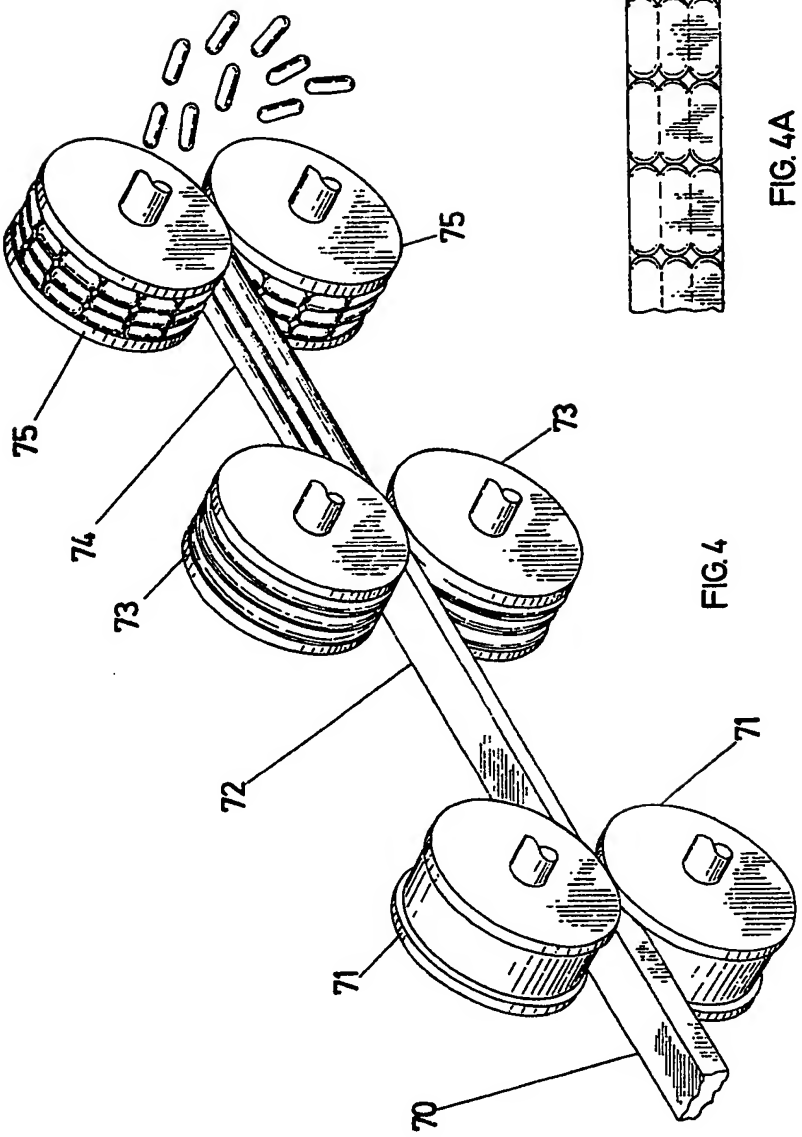


FIG. 4

FIG. 4A

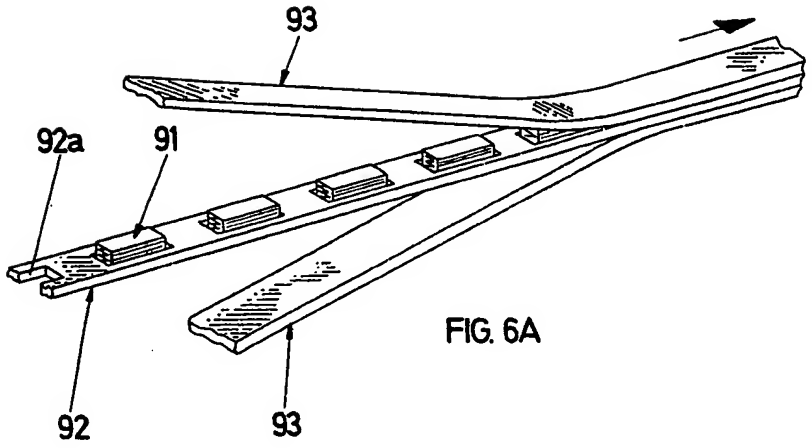


FIG. 6A

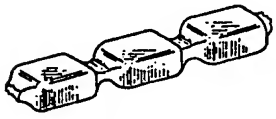


FIG. 6B

FIG. 6C

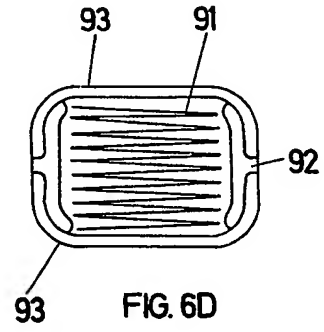
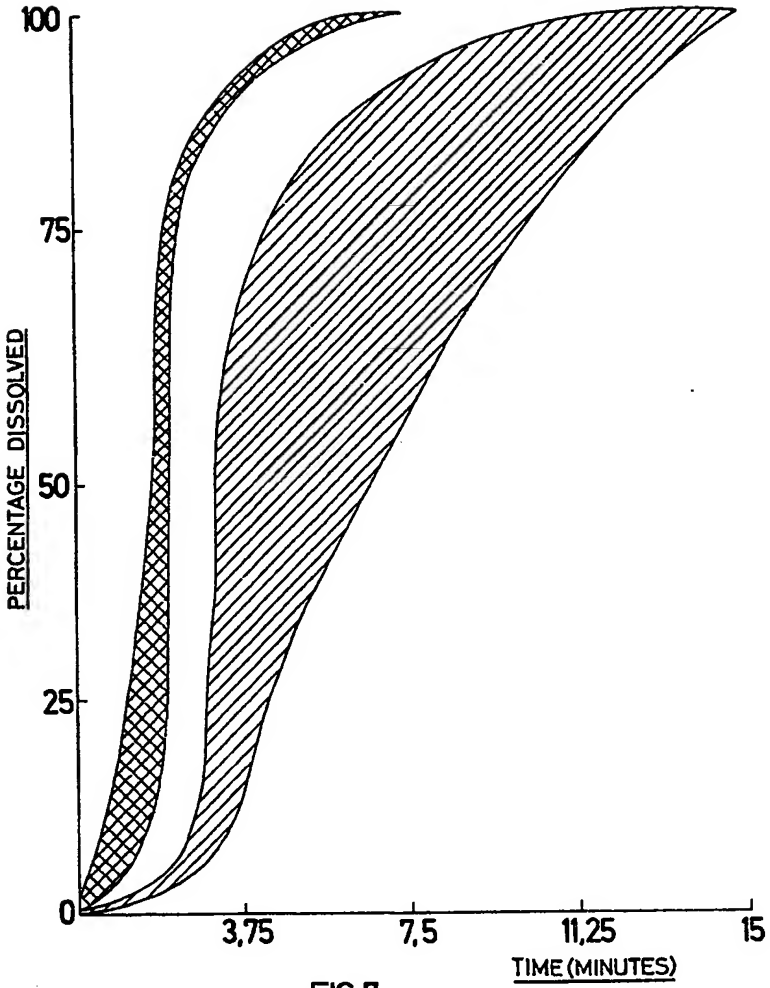


FIG. 6D


100
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50
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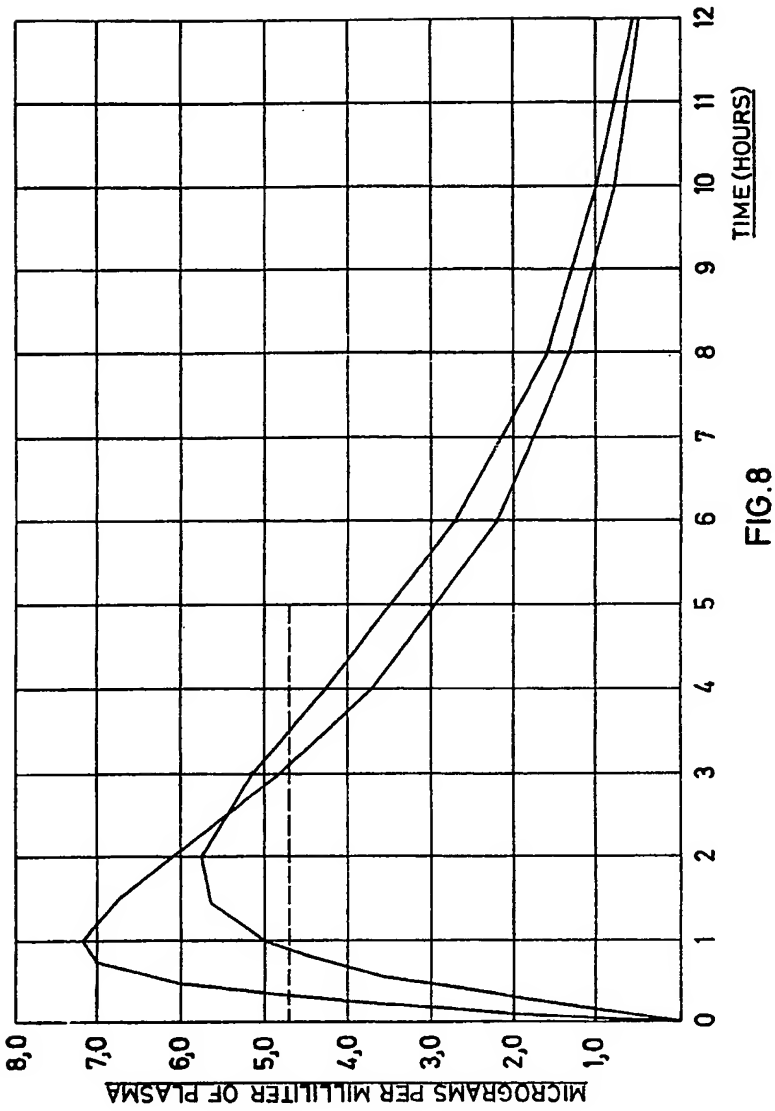
PERCENTAGE DISSOLVED
3,75
7,5
11,25
15
TIME (MINUTES)

FIG.7


MICROGRAMS PER MILLILITER OF PLASMA
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1
2
3
4
5
6
7
8
9
10
11
12
TIME (HOURS)

FIG.8